2015 CSF Colloquium Proceedings:

Mechanisms and Pathophysiology of Headache in the Population of Patients with Chiari Malformation and Hypermobility Connective Tissue Disorders

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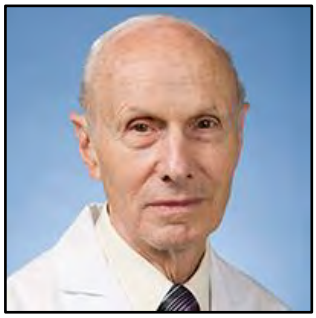
Dedication

Dedicated to the improved diagnosis and treatment of patients with Chiari malformation, syringomyelia, and the related disorders.

Contents

The Contributors



Ulrich Batzdorf, MD received his medical education at New York Medical College, where he also served as Instructor in the Department of Biochemistry. His postgraduate training included two years of general surgery at the University of Maryland, neurology training at the National Hospital, Queen Square, London, a neuropathology fellowship at the University of California, San Francisco and neurosurgical training at the University of California, Los Angeles (UCLA).

He has been on the faculty at UCLA since 1966, where he currently is a Professor in the Department of Neurosurgery. Dr. Batzdorf's interest in syringomyelia, Chiari malformationand related disorders dates back over 30 years and has included clinical research resulting in numerous publications, book chapters, as well as editing of a book on syringomyelia and a Handbook for Patients and their Families.

Paolo A. Bolognese, MD, A native of Torino, Italy, M.D., graduated cum laude from the Medical School of the University of Turin. In 1990, he completed his neurosurgical training at the same university under the guidance of Professor Victor A. Fasano, an international leader in the field of high-tech applied to neurosurgery.

During this time, Dr. Bolognese became the leading worldwide expert in the field of laser Doppler flowmetry applied to neurosurgery and the top European figure in the field of neurosurgical intraoperative ultrasound. Upon the death of his former mentor, in 1992 he accepted the invitation of Dr. Thomas H. Milhorat to transfer his laser Doppler research to the United States and to be retrained under Dr. Milhorat at SUNY Health Science Center at Brooklyn. In addition to his U.S. neurosurgical training, Dr. Bolognese became the first trainee of the Fellowship in the Surgical Management of Chiari I Malformation and Related Disorders under Dr. Milhorat.

In 2001, Dr. Bolognese joined Dr. Milhorat at the Departments of Neurosurgery at North Shore University Hospital and Long Island Jewish Medical Center and as Associate Director of the Chiari Institute. Dr. Bolognese is the Director of the Chiari Neurosurgical Center at Neurological Surgery, P.C.

Curtis W. Dewey, DVM, MS is an associate professor and section head of Neurology/Neurosurgery at the College of Veterinary Medicine, Cornell University, Ithaca, NY. He is a diplomate of both the American College of Veterinary Internal Medicine (neurology) and the American College of Veterinary Surgery. Dr. Dewey is the author of "A Practical Guide to Canine and Feline Neurology," a recognized textbook of veterinary neurology and is currently working on the second edition. He has lectured on varied veterinary topics including vestibular and cochlear nerve damage, disorders of the brain, selected encephalopathies, Myesthenia Gravis, seizure control, spinal cord disorders, head trauma and disc disease.

Dr. Dewey graduated from Cornell University, where he received both his Bachelor of Science and Doctor of Veterinary Medicine degrees. He completed a one-year internship in small animal medicine and surgery at the University of Georgia College of Veterinary Medicine. Following his internship, he completed a three-year comprehensive surgical residency at the University of Georgia College of Veterinary Medicine and earned a Master of Science degree in anatomy.

At the University of California College of Veterinary Medicine, he completed a two-year comprehensive residency in neurology and neurosurgery. He has been on the teaching staff at the College of Veterinary Medicine of Texas A&M University, School of Veterinary Medicine and at Long Island Veterinary Specialists.

Dr. Dewey has lectured regionally, nationally and internationally and has authored and collaborated on hundreds of scientific articles published in peer reviewed journals and in abstracts and proceedings. Many of his research projects such as Genetic Alterations in Canine Astrocytomas have been funded and presented at national conferences. He holds membership in a number of professional organizations and is on the editorial board of several medical journals.

While on staff at Long Island Veterinary Specialists, he and Dr. Dominic Marino pioneered the surgical procedure, Foramen Magnum Decompression with Cranioplasty to address the condition known as Chiari like malformation in dogs. He is an internationally recognized authority on veterinary neurology and continues to study naturally occurring diseases while on staff at Cornell University. His other interests include Tae Kwon Do (3rd degree black belt), Kung Fu (red sash), running, swimming and camping. His extensive understanding of the facets of veterinary medical and surgical neurology and the study of naturally occurring diseases will help contribute to the mission of the foundation.

Dr. Clair Francomano, MD attended Yale College as an undergraduate and received her M.D. from Johns Hopkins University School of Medicine. She trained in Internal Medicine and Medical Genetics at Johns Hopkins and joined the full-time Hopkins faculty in 1984. In 1994 she became Chief of the Medical Genetics Branch at the National Human Genome Research Institute, National Institutes of Health, where she served as Clinical Director from 1996-2001. From 2001-2005 she was Chief of the Human Genetics and Integrative Medicine Section in the Laboratory of Genetics, National Institute on Aging. She joined the GBMC faculty in 2005 as Director of Adult Genetics at the Harvey Institute of Human Genetics, and joined the GBMA practice in July 2006.

Fraser C. Henderson Sr., MD was foreman on a cattle station in the Outback of Australia before receiving his Bachelor's and Medical degrees at the University of Virginia, Charlottesville VA. He served with the Multi-National Peace Keeping Force in Beirut, earning the Navy Commendation Medal for treatment of mass casualties following the terrorist bombing attack in Beirut, Lebanon, October 1983. After completing his residency under Phanor Perot at the Medical University of South Carolina, he returned to Bethesda Naval Hospital as Director of Spine. In 1990-1991, he was Brigade Neurosurgeon for the 4th Marine Expeditionary Brigade in Desert Shield and Desert Storm during the 1st Gulf War. He then completed a fellowship in Craniospinal surgery under Professor Alan Crockard at The National Hospital for Neurology and Neurosurgery, Queen Square, London. Commander Henderson then joined Georgetown University as Director of Spine and Cranio-cervical Junction.

In 2005, he was promoted to Professor of Neurosurgery, and Associate Professor of Radiology, and was active in advancing CyberKnife radiosurgery for treatment of complex spinal tumors. He was Co-Director of the Lombardi Neuro-Oncology Division, Co-Director of the CyberKnife Radiosurgery Center and Medical Director of the Neuroscience ICU and nursing units. He developed intellectual property for spinal radiosurgery, spinal cancer, and was Principal Investigator in development of a radio-sensitizing drug, and a drug to block the malignant invasiveness of Glioblastoma Multiforme. In 2007, he received the AANS/CNS Award for Excellence in Spine Research in 2007.

Dr. Henderson entered private practice in Chevy Chase, Maryland, as Director of Neurosurgery at Doctors Hospital and Director of the Chiari Syringomyelia Foundation Greater Metropolitan Washington Chapter, where he is focused on the development of the understanding and treatment of deformity induced injury to the brainstem and spinal cord in Chiari Malformation and Ehlers Danlos Syndrome.

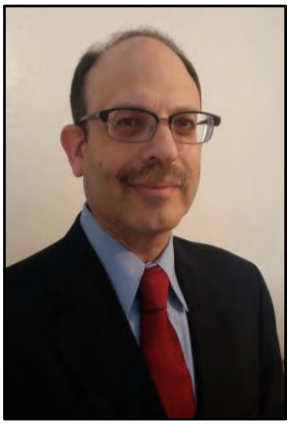
He was recipient of the Annual Physicians award at Shady Grove Adventist Hospital in 2011, and received an honorable mention as a Schwartz National Award for Compas-

sionate physician. He holds 14 patents for devices, has published 55 peer reviewed articles and book chapters, presented over 140 abstracts and invited lectures, and has served as guest editor for several spine journals. He currently serves on the Executive Board of the CSF, EDNF, the ILC and TCAPP foundations and is the EDSI Committee Chair for Neurological Manifestations of EDS. Dr. Henderson lives with his wife, Becky, and their three sons - Fraser, Lansdale and Landon - on a farm in Prince George's County, Maryland.

Dr. Petra M. Klinge, MD, PhD received her medical degree at the University in Kiel in 1993. After completing her neurosurgical residency in Hanover Medical School, Germany, in 2002, Dr. Klinge held the position of Senior Physician and Assistant Professor of Neurosurgery at the International Neuroscience Institute in Hanover, Germany. Dr. Klinge joined the Neurosurgery Foundation and the Warren-Alpert Medical School at Brown University, Providence, Rhode Island, as an Attending Neurosurgeon in May 2009 and received the degree of Associate Professor of Neurosurgery at the Warren-Alpert Medical School at Brown University in December 2009.

Dr. Klinge is an internationally renowned clinician for diagnosis and neurosurgical treatment of patients with Hydrocephalus and Alzheimer dementia. She continues her research activities in collaboration with the Department of Clinic Neurosciences at Brown University, working on the unifying concept of dementias, in particular Alzheimer-related pathology in Hydrocephalus of aging patients. In addition to complex adult and pediatric hydrocephalus, her practice also includes skull-base surgery and patients with developmental Cerebrospinal fluid disorders such as spina bifida, Chiari malformation, as well as both benign and malignant tumors of the brain. As a trusted advisor and resource on hydrocephalus research, Dr. Klinge also speaks on the behalf of the Hydrocephalus Association (HA) at NIH-sponsored workshops and national and international conferences. Dr. Klinge's scientific interests comprise the development of advanced techniques for diagnosing and treatment of dementia, experimental work to advance the understanding of normal aging, cerebrospinal fluid circulation and dementia, and development of novel biotechnical treatment approaches, including stem cell therapy for the treatment of cerebrospinal fluid disorders and neurodegenerative diseases.

Dr. Klinge was President of the International Society for Hydrocephalus and CSF Disorders from May 2010 to 2012, and is currently an active member of the American Association of Neurological Surgeons and the Congress of Neurological Surgeons.



Myles Koby, MD is the staff Neuroradiologist at Doctors Community Hospital of Prince Georges County of Maryland. He has been an Assistant Professor at the University of Maryland School of Medicine and staff Neuroradiologist Department of Diagnostic Radiology, National Institutes of Health Bethesda, Maryland.

He completed his neuroradiology fellowship at Mallinckrodt Institute of Radiology, Washington University School of Medicine, Saint Louis, Missouri and Residency in Diagnostic Radiology at Los Angeles County/University of Southern California Medical Center, Los Angeles, California. He is a graduate of Wayne State University School of Medicine, and University of Detroit School of Dentistry, both in Detroit, Michigan. He has been a reviewer for JCAT (Journal of Computer Assisted Tomography).

David Limbrick, M.D., Ph.D., is a pediatric neurosurgeon at St. Louis Children's Hospital, Washington University in St. Louis. Dr. Limbrick graduated with a B.S. (Biology) from the College of William and Mary as well as an M.S. (Physiology), Ph.D. (Pharmacology) and M.D. from the Medical College of Virginia. His graduate research training was in cellular neurophysiology in the laboratory of Dr. Robert DeLorenzo and in molecular biology in Joshua Rubin's lab at Washington University.

Dr. Limbrick's clinical interests include epilepsy surgery, hydrocephalus and surgery of the craniovertebral junction. His research has focused on cerebrospinal fluid physiology in the setting of developmental brain injuries and syringomyelia. He is currently an Assistant Professor of Neurological Surgery and Pediatrics.

Dr. Andreas Linninger, PhD is a Professor of Bioengineering at the University of Illinois at Chicago. His research interests include hydrocephalus, synthesis of magnetically guided nanoparticle platforms, intrathecal drug delivery, and hemodynamics.

Dr. Linniger holds a PhD in Chemical Engineering from the Vienna University of Technology, in addition to degrees in Business Management Education from the Vienna University of Economics and a Diploma in Chemical Engineering from the Vienna University of Technology. Dr. Linniger served as a Postdoctoral Fellow at the University of California at Berkeley and a Postdoctoral Research Associate at the Massachusetts Institute of Technology.

Dr. Mark Luciano, MD, PhD is the director of the Johns Hopkins Cerebral Fluid Center. A renowned leader in treating hydrocephalus, Dr. Luciano is distinguished both nationally and internationally for his research and educational and clinical work in neuroendoscopy. Dr. Luciano treats adults with hydrocephalus, pseudotumor cerebri, intracranial hypotension, Chiari malformations, and cerebral and spinal cysts. He has significant expertise treating children and adults with cerebrospinal fluid leaks and congenital disorders.

Among his accomplishments in neuroscience research and biomedical engineering are his investigation of the cerebrovascular response to hydrocephalus and the invention of a unique device for control of intracranial pressure (ICP) pulsatility to increase blood flow. His National Institutes of Health-funded studies have explored prolonged compression and hypoxia in the brain as a result of hydrocephalus, as well as the interaction between cerebrospinal fluid and vascular systems.

Anne Maitland, MD, PhD was named one of New York Times 2011 Super Doctors and one of America's Top 21 Women's Doctors by Lifescript.com in 2009. She is a Fellow of the American College of Allergy, Asthma and Immunology and a member of the American Academy of Allergy, Asthma and Immunology.

Dr. Maitland is very active in local societies and the surrounding communities, to increase awareness of immune mediated disorders. She is also involved with research to continually improve the treatments of allergies, asthma and recurrent infections. Her clinical focus includes the diagnosis and treatment of allergic skin disorders, allergic rhinitis (hayfever), drug allergies, food allergies/sensitivities, asthma and recurrent infections.

John E. Mitakides, DDS, DAACP has made improving the quality of life for people living with TMJ and craniofacial pain his life's work. He is a nationally-recognized expert in the field of TMJ disorder and craniofacial pain. Additionally, Dr. Mitakides is a leading expert in craniofacial pain and TMJ disorder in the Ehlers-Danlos Syndrome (EDS) patient.

Dr. Mitakides is a Diplomate of the American Academy of Craniofacial Pain, one of only 115 practitioners in North America to earn that recognition. He is a Diplomate of the American Board of Craniofacial Dental Sleep Medicine, and a

member of the Professional Advisory Network of the Ehlers-Danlos National Foundation, the leading organization serving EDS patients and physicians. In addition, he is the only dental professional serving as consultant to the new Ehlers-Danlos National Foundation Center for Clinical Care and Research in Baltimore.

Located near Dayton, Ohio at the TMJ Treatment Center, Dr. Mitakides leads a highly-trained and qualified team of professionals, including TMJ certified assistants, offering patients complete dental care.

Dr. Mitakides is a graduate of The Ohio State University Dental School and has been a practicing dentist for 40 years, licensed in Ohio, Texas and Maryland. He is on staff at both Kettering Medical Center and Cincinnati Children's Hospital.

Dr. Mitakides is a frequent lecturer at national and international conferences, presenting TMJ and Craniofacial Pain diagnosis and treatment techniques he has developed. He also presents lectures for higher and continuing education courses, and has served as an expert witness for legal cases related to trauma and accidents resulting in TMJ and craniofacial pain.

Dr. Sunil J. Patel, MD is a Professor and the Chairman of the Department of Neurosurgery at the Medical University of South Carolina. Dr. Patel is an experienced and accomplished neurosurgeon with 30 years in clinical practice.

Dr. Patel earned his medical degree from the Medical University of South Carolina. He completed his internship and residency in neurological surgery at the Medical University of South Carolina as well as fellowships in Microneurosurgery and Skull base Surgery at the University of Pittsburgh, PA and Cerebrovascular Surgery at Nagoya University School of Medicine, Japan. He is affiliated with the Medical University of South Carolina and Ralph H. Johnson Veterans Affairs Medical Center.

Dr. Patel is a prolific researcher, having been investigator in NIH funded research on Hypertension and several clinical trials. He has authored a multitude of peer-review publications. He is board certified by the American Board of Neurological Surgery.

Harold L. Rekate, MD, FACS, FAAP is currently the Director of the Chiari Institute Professor of Neurosurgery at the Hofstra Northshore LIJ School of Medicine. Dr. Rekate served as chairman of pediatric neurosciences and chief of pediatric neurosurgery for more than 25 years at the Barrow Neurological Institute (BNI). While at BNI, Dr. Rekate was a clinical professor of neurosurgery at the University of Arizona College of Medicine.

Dr. Rekate completed his undergraduate studies at Duke University and received his medical degree at the Medical College of Virginia. He trained in neurosurgery and pediatric neurosurgery

at the University Hospitals of Cleveland and completed his residency training at Case Western Reserve University. Dr. Rekate is board certified by the American Board of Neurological Surgery and the American Board of Pediatric Neurological Surgery.

A widely published author of more than 200 publications, most of which are related to cerebrospinal fluid difficulties, including Chiari malformations, syringomyelia and hydrocephalus, Dr. Rekate also served as editor for a number of prestigious medical journals and was chairman of the editorial board of the Journal of Neurosurgery Pediatrics. Over the course of his career, Dr. Rekate has done extensive research regarding spinal fluid flow, receiving funding from the National Institutes of Health and the National Aeronautics and Space Administration.

He also has held many local, national and international positions, including chairman of the Joint Section on Pediatric Neurological Surgery of the American Association of Neurological Surgery and the Congress of Neurological Surgery, and president of the American Society of Pediatric Neurological Surgeons and the International Society of Pediatric Neurosurgery. Dr. Rekate has received numerous awards and honors, including the prestigious Pudenz Award of Excellence in Research in Cerebrospinal Fluid Physiology.

Recently, Professor Rekate has been appointed to serve as advisor to the National Aeronautics and Space Administration on problems related to visual impairment in astronauts spending long periods of time in space. He has also been instrumental in the formation of the International Hydrocephalus Imaging Working Group (IHIWG). This group represents the first attempt to bring together researchers, engineers, neuroradiologists and clinicians to study hydrocephalus specifically related to new MRI technology and mathematical modeling.

Dr. Peter Rowe, MD is a Professor of Pediatrics at the Johns Hopkins Children's Center in Baltimore, Maryland. He graduated from the McMaster University Medical School, Hamilton, Ontario, Canada, in 1981. From 1981 to 1987, he was a resident, General Academic Pediatrics research fellow, and Chief Resident in Pediatrics at the Johns Hopkins Hospital. Between 1987 and 1991 he was a staff member at the Children's Hospital of Eastern Ontario, Ottawa, Canada, and an Assistant Professor of Epidemiology and Community Medicine, and of Pediatrics.

Dr. Rowe returned to Johns Hopkins University in 1991. He has published over 60 peer-reviewed papers, 10 book chapters, and edited the 11th edition of the Harriet Lane Handbook. His clinical interests have been in the area of diagnostic dilemmas and complex chronic illness. He directed the Johns Hopkins Children's Center Diagnostic Referral Clinic from 1991 to 1997. His early research interests were in the general area of clinical epidemiology in Pediatrics, but in the past 20 years his work has focused more exclusively on conditions characterized by chronic fatigue.

His work first described the relationship between chronic fatigue syndrome (CFS) and treatable orthostatic intolerance syndromes, and first reported the association between Ehlers-Danlos syndrome and CFS. The research has been funded by the National Institutes of Health, the US Department of Defense, the CFIDS Association of America, and several smaller foundations, as well as by private philanthropy. He has directed the Chronic Fatigue Clinic at the Johns Hopkins Children's Center since 1996, where he is the inaugural recipient of the Sunshine Natural Wellbeing Foundation Chair in Chronic Fatigue and Related Disorders.

Preface

This text is the compilation of presentations delivered in September 2015 at the Chiari and Syringomyelia Foundation (CSF) Colloquium in New Orleans, Louisiana. The Colloquium discussion focused on "Mechanisms and Pathophysiology of Headache in the Population of Patients with Chiari Malformation and Hypermobility Connective Tissue Disorders." Representative and important slides accompany the text, which has been faithfully transcribed from recordings of the delivered remarks. Each "chapter" represents each speaker in the same sequential order in which he or she spoke.

Introduction

Treatment of Chiari malformation has remained a "minefield" for many surgeons, because of the many co-morbid conditions that complicate the diagnosis, treatment and outcomes of treatment. The following, though by no means encyclopedic, draws upon the aggregate experience from many disciplines and perspectives, in different parts of the globe, in its discussion on the Mechanisms and Pathophysiology of Headache in Patients with Chiari Malformation and Hypermobility Connective Tissue Disorders. Beyond the technical considerations of Chiari surgery, the editors believe that the Chiari Malformation serves as a portal to understanding, and hopefully addressing, formidable genetic, vascular, immune and neurophysiological challenges. These broad perspectives do not bring us to a conclusory understanding of Chiari and associated disorders, but rather represent a very nascent recognition of what lies ahead.

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1. Summary of 2014 Colloquium Proceedings

DR. ULRICH BATZDORF, MD

I promise to be very brief. The symposium last year was entitled Colloquium on Comorbidities of Chiari Malformation. And as I listened to today's proceedings, I began to come to the idea that maybe Chiari is, in fact, a comorbidity of many other disease entities. Perhaps we need to think of this slightly differently.

The publication for the 2014 book, let me say, is currently in the process of being revised a little bit and will be out and available shortly. However, there were essentially three different comorbidities discussed last year, during the 2014 Research Colloquium.

One such condition was hypermobility at the craniocervical junction. A second comorbidity was pseudotumor cerebri otherwise known as idiopathic intracranial hypertension. And a third was tethered cord syndrome. Common to all of these comorbidities was the need for them to be considered during the pre-operative evaluation of a Chiari patient before undergoing surgery. All three have the potential of adversely affecting the outcome of surgery for Chiari malformation if they fail to be recognized before surgery.

Hypermobility at the craniocervical junction implies a degree of abnormal laxity of the ligaments and muscles at this level. This may result from flexion-extension injury or so-called whiplash injury, as was discussed last year by Dr. Long; and it may result from connective tissue disorders, as was discussed by Dr. Francomano.

The frequency of unrecognized hereditary connective tissue disorders in the Chiari population has certainly been underestimated, particularly when one considers not only a history of unusual flexibility, as mentioned using the example of the Rockettes, but also when one considers autonomic symptoms manifested as postural orthostatic hypotension and related states of dysautonomia, which may lead to altered sympathetic innervation of the lower limbs in the standing position, as Dr. Rowe discussed so beautifully. Dr. Rekate also demonstrated this hypermobility in his presentation of his patient with the Sara syndrome. Dr. Koby also pointed out the difficulty of identifying such ligamentous problems by currently available imaging studies, such as CT and MR scanning.

Of great interest is the concept that there may be a genetic difference between the Chiari patients with a connective tissue disorder and those without, as Dr. Ashley-Koch presented, showing that there were genetic indicators on chromosome 1 (TGF-β2) and on chromosomes 8 (GDF6) and 12 (GDF) in the patients with connective tissue disorders. The data again points out to some genetic differences that, I think, we will learn to explore to a greater degree as the years go by.

Related to this entire topic was the shared problem of actual versus potential instability at the craniocervical junction, in what Dr. Doug Brockmeyer called the complex Chiari patient, notably, those patients with basilar invagination. Common to all of these patients with ligamentous instability, including connective tissue disorders and complex Chiari cases with basilar invagination, is that the standard posterior fossa decompression may, and often does, increase the instability by disrupting the posterior tension band and weakening the axial musculature.

And it is, I think, in part, for this reason that innovative surgical approaches such as were described by Dr. Liu and Dr. Bolognese have an appeal because what we need to

do is to work on ways to minimize the disruption of the posterior supporting structures in these patients who already have a hypermobility problem, whether due to connective tissue disorder or whether due to something like basilar invagination or a retroflexed odontoid.

Neuropathic pain may also be common in these patients. Dr. Long discussed the possibility of central pain sensitivity. The management of these patients may be further complicated by a fact that Dr. Luciano pointed out: even in seemingly identical patients, the motion of cerebellar tonsils against the cervicomedullary junction may not be identical. This consideration is certainly something that we need to investigate further.

Pseudotumor cerebri, the second comorbidity discussed last year, was described in great detail by Dr. Rigamonti. Again, the problem was alluded to in a discussion today: it is not absolutely certain whether pseudotumor causes tonsillar descent, or whether tonsillar descent may be responsible for the increased intracranial hypertension that one observes in pseudotumor patients.

Dr. Petra Klinge led a discussion of the third discussed comorbidity: tethered cord syndrome. She built on that discussion today. Certainly, tethered cord syndrome should be considered as a comorbidity in patients with Chiari malformation. Symptoms that she described and on which we were able to come to consensus, were low back pain, leg pain and weakness with sensory deficits, and, very often, urinary and bowel dysfunction. The findings on examination that she has asked us to take home were leg weakness, sensory impairment in the lower extremities, a diagnosis of neurogenic bladder, preferably confirmed by urodynamic testing, radiological assessment with a suggestion of tethered cord syndrome ruling out other possible causes of the same type of symptomatology, and ruling out other medical issues that might be the cause.

Finally— and I promised to be brief— there was, at least, a consensus statement on our prior discussion of what would be considered a normal or abnormal clivo-axial angle. It was decided that anything less than 135 degrees would be abnormal. We concluded that a Grabb-Oakes measurement of more than 9 millimeters would be considered abnormal. We felt that the basion-axis interval of over 12 millimeters was abnormal.

I give you these figures with the understanding that it is, in fact, very difficult to get a consensus on these measurements. I see smiles in the audience from people who probably disagree. But those were the main messages that I carried away from last year's meeting. Thank you very much.

Discussion Following presentation

DR. DONLIN LONG: Fraser, are you going to close? Do we have other information?

DR. FRASER HENDERSON: We had talked about forming a consensus on tethered cord symptoms.

DR. BATZDORF: Well, I'm trying to summarize this, and not take it out of proportion of the rest of the discussion. I actually reviewed what Petra gave me.

DR. HENDERSON: I see.

DR. BATZDORF: If you want to elaborate on that, please do. Or if Petra does?

DR. PETRA KLINGE: The question is regarding what we designed yesterday. Should we distribute our conclusions and ask people for opinions? Or how do you think we should–

DR. HENDERSON: I think that would be a great idea. Let's send that around and see what everyone thought.

Basically, it's simply what we consider tethered cord syndrome to be: the presenting symptoms, findings, and diagnostic studies. I don't think that the statement we came up with is very controversial at all. It collates what we know from all the literature. I think it just brings everyone onto the same page about what exactly is tethered cord. I believe that if many people who have taken a very negative perspective of occult tethered cord syndrome look at this document, they'll realize that we're really all on the same page and that there's very little we disagree about.

MS. DOROTHY POPPE: So can we send via e-mail like we did with the clivo-axial angle, and get a consensus that way?

DR. HENDERSON: Yes.

MS. POPPE: Thank you all very, very much.

2. Cervico-Medullary Syndrome: Observations & Questions

DR. PAOLO A. BOLOGNESE, MD

Thanks a lot for having me here. It is always not just an honor, but a real pleasure to get together with so many stimulating minds, especially when meeting about this topic for which we all have such a passion.

Cervicomedullary syndrome is a term that we all agreed upon two years ago when we had the second-to-last CSF Research Colloquium. It was one of the parts of the consensus. Today I am just going to make some observations, in a very free style of presentation, with some questions at the end. I also apologize because I am sleep-deprived, I slept about five hours in the last three nights; so I apologize for any potential incoherent blabbering I'm going to have. I have no disclosures.

The definition of cervicomedullary syndrome (CMS) is a clinical entity caused by the involvement of the lower brainstem and the upper spinal cord. That is the agreement that we had reached— very generic. There are a number of different pathologies that may cause it; pathologies that clinically affect the area of the cervicomedullary junction. So, for our group, obviously, our focus is more on Chiari malformation and craniocervical instability-related disorders. Obviously, many other pathologies in the same area can cause a similar kind of syndrome and symptomatic presentation.

We see updates every once in a while from Dr. Ashley-Koch at Duke and, as we heard this morning, their lab has recently shown that there is actually a difference at the genetic marker level[1] between the patients with Chiari alone, and the patients with Chiari and Ehlers-Danlos syndrome (EDS)— the former set of patients being very close to the genetic phenotype of people with Klippel-Feil.

So Chiari, EDS, Klippel-Feil: they appear to have a common mesenchymal ancestry. So the next logical question is, since we very often find mast cell activation disorder and mitochondrial disorder in these patients and their children as well: are they coming along with the ride? Is there a similar mesenchymal ancestry there, too?

Pathophysiologically, what greatly concerns our group is more or less a compression/distortion game. Obviously, if you have an ischemic lesion, inflammatory lesion, intrinsic tumor in the same cervicomedullary junction, you are going to end up having similar presentations.

But of the compression and distortion that characterizes this class of pathology or group of pathologies, the first and most popular is that of the mass effect exerted by the tonsillar herniation from posterior towards anterior on the cervicomedullary junction. I introduce another complicating factor as there may also a component of neurovascular compression.

Neurovascular compression has been something that has been talked over and over regarding the seventh cranial nerve. I wonder if the eleventh cranial nerve, the ninth, the tenth can also be affected in the case of the problematic small posterior fossa and any bulky tonsils.

The tonsils also can be symmetric— sometimes they are symmetric. They are triangular, they are rounded; and obviously, their mass effect is heavily influenced by their shape and lack of asymmetry.

Anteriorly, there is a Grabb measurement and clivo-axial angle (CXA) to further quantify our pathologies. The Grabb measurement appears to quantify the anterior mass effect from these structures, while the CXA better describes the angular distortion that these structures are exerting on the nervous system. This distortion can be static, dynamic, or combined.

Tonsillar herniation is then another problem per se. Many people who are obviously not in this room since it is comprised of mainly experts will equate tonsillar herniation automatically with Chiari I malformation. This is often the mistake of a newbie. A neophyte finds tonsillar herniation, thinks it is a Chiari, tackles it as a Chiari, and then many of the neurosurgeons in this room pick up the pieces.

So, once again, tonsillar herniation can come from many different causes. These causes were qualified by an article from Dr. Milhorat in 2010[2] on which Dr. Kula was a coauthor. Tonsillar herniation can be described in a very pedestrian way, as resulting from four mechanisms: pushing, pulling, dangling, and squeezing. The squeeze represents the small posterior fossa of the typical Chiari I malformation.

The complex Chiari is a kind of new concept. There is this brainstem sandwich, where there is tonsillar herniation from behind and there is anterior pathology, dynamic and/or static, from the front. There is a medullary kink. And all these things are contributing to a specific modulation of the syndrome. So if the Chiari I compression comes mostly from behind, the complex Chiari has an anterior and a posterior component, which brings along with it a different modulation of the syndrome.

One thing that every now and then I have to remind myself is that even if there is a gravity component on the skeleton, the reality is that the cerebellum is not really affected by gravity in the same way as the skeleton. Number one, the cerebellum is suspended inside the dura, inside the cerebrospinal fluid; so there is a sort of buoyancy and floating component. The other thing to recall is that the cerebellum is attached to the brainstem by three solid peduncles and where one goes, also the others tend to go.

Also in the complex Chiari there is sometimes an even, or uneven balance between the anterior and the posterior compression. Recently there was a controversy stirred up by Dr. Goel[3] who went on to say that, in his opinion, the Chiari I malformation was secondary to anterior pathologies, which were distorting the brainstem downwards and backwards.

No one in this room marries that conclusion, but indeed there are some forces from anterior and posterior that tend to get the cervicomedullary junction in the middle, no matter how we want to represent it terminologically.

From a symptomatological standpoint, there are multiple symptoms because it is a busy area. There are a bunch of cables, bunch of centers; so, obviously, there is not going to be just one function that is affected. Anterior pathology alone is going to create selective compression— well, not "selective" but predominant compression on the anterior centers, while the posterior pathology is going to affect something different.

At last year's Colloquium, we discussed comorbidities of Chiari I malformation beyond Chiari I and EDS. So besides postural orthostatic tachycardia syndrome (POTS), pseudotumor cerebri and tethered cord, many of us have had patients present with mast cell activation disorder or even mitochondrial disorders. So all these issues are found in these patients, and it is unclear if they present as accidental partners in crime, or intentional partners in crime.

I am now going to breakdown a few clinical concerns not so much to reinvent the wheel and explain them again, but just to show how all these issues linked together by the cervicomedullary syndrome umbrella may sometimes be confusing since there are many contradictory or compounding factors.

Headaches can have a positional component; okay, so far so good. Cranial settling and craniocervical instability are easy to understand. We heard this morning from Dr. Luciano and Dr. Rowe about intracranial hypotension and POTS, respectively.

There is also the problem with over-shunting. Some of these patients have pseudotumor, they have accumulated hydrocephalus or they have a complication from cerebrospinal fluid leakages. Many of the surgeons have hardware that have been invented and designed for hydrocephalus, and when they place the shunt in some of these patients, the shunt is really struggling out of its own element. The correction that the shunt is seeking to make is not exactly the purpose for which it was intended, so very often these patients are over-shunted.

Now, when you have a patient with positional headaches with the unfortunate luck of having all these four elements: EDS, some leakage from former lumbar punctures, cranial settling, some POTS elements because they're dysautonomic, and maybe they also have a shunt or they are over-shunted— where exactly do we as neurosurgeons begin to fix this patient?

In relation to cerebrospinal fluid pressure, again we have been previously taught with MRIs showing us the anterior and posterior blockage. I remember the first MRI that I ever saw as a resident was an MRI coming from UCLA. We were all envying Dr. Batzdorf, who was playing with such a wonderful toy. Seeing that blockage not only was the epitome of the phrase "seeing is believing," but it also provided a better understanding at a visceral level.

Now, it is known that people with Chiari I malformation have problems with flow. Some of them also have cerebrospinal fluid pressure problems that may persist in the aftermath of the decompression.

Some patients have hydrocephalus as a cause of the tonsillar herniation. So in retrospect, that is not a pure Chiari. However, in other cases, a patient can have a Chiari which is so tight that it is compressing the fourth ventricle as you would expect to see in hydrocephalus. So you do not necessarily know which is the chicken and which is the egg.

In even further patients, there may be a presence of pseudotumor along with minimal rounded herniation in the presence of a normal posterior fossa. A newbie will go into surgery and say, "That is a Chiari; do the decompression." He ends up with a proverbial egg on the face because there is a leak. The surgeon will then have the belated knowledge that the patient had 70 cm of water or CSF and then a bunch of other reoperations on his hands.

Other times, the patient has a leakage after decompression, an aseptic meningitis; and as a late aftermath of that, besides the pseudomeningocele, there can be a development of this pseudotumor or cerebral-like syndrome, in which the pressures are not up to 70 or 80, but they are about in the 30s. This syndrome which did not exist before can make the patient cranky but it may be ameliorated by serial taps and/or shunting.

Regarding cerebrospinal fluid pressure, we have accumulated some other observations over the years. For instance, some of these patients have abnormal compliance.

Some patients have decreased reabsorption; we will incidentally find an increased pattern in the cerebrospinal fluid spaces in T2 over the vertex by the arachnoid granulations. With EDS, similar to what Dr. Luciano was stressing this morning, we have found dural blebs, leaks, and cysts.

There is also the roller coaster of a patient with pseudotumor and EDS. At the point when the pressure goes up, the abnormal compliance associated EDS creates all these blebs— the bleb can explode when the patient has an extra burst with a Valsalva, there is a minor leakage and the pressure goes down. The patient develops intracranial hypotension from the pseudotumor prior, and then either Mother Nature or a neurosurgeon fixes the leak. The patient will wind up coming back over and over again for a pressure that is highly variable, up and down.

It is very difficult to handle at that point. Dr. A will encounter the patient when the pressure is up, and treat him one way; while Dr. B thinks that Dr. A is wrong because he measures the pressure much lower somewhere down the road.

In terms of blood pressure, we have seen the elements of POTS, EDS, the brainstem, the veins– I am not going repeat what Dr. Rowe has already elucidated– so I will forgo repeating this, other than pointing out the following.

First discovered by Dr. Milhorat in 1999, Chiari is frequently associated with arrhythmias, SVTs, and tachycardia, sinus tachycardia being the most frequent. And, obviously, when tachycardia goes out of control, it can have a direct effect on the blood pressure.

Then there is the frequently encountered problem with adrenal insufficiency. I once discovered this the hard way. Dr. Batzdorf and I once had a patient who was this big, gangly and tall guy who was about 6 feet eight— in retrospect, he probably had some Marfanoid features.

We gave him a small course of steroids after his surgery as was the standard practice—just a short course of steroids with Decadron, easy in/easy out. We began to notice, however, that the patient was really, really sick. So we hurried to get some imaging but found that there was no leakage, nothing obvious. We tried to check him for everything under the sun.

The local neurologist gave him a touch of steroids again because that is what most neurologists do– except Dr. Kula, who is much more particular than that. After two or three courses, all us geniuses finally figure out that the patient had adrenal insufficiency.

That case inspired me do a PubMed search, and I found an article describing the people with EDS had the selective vulnerability with their adrenal glands.[4]

After finding that article, I have seen probably 12 to 15 of my patients fit this description. In fact, the last patient is still in the hospital now with this. The last one had a very nice course. All of a sudden, she developed cerebral salt wasting after pedestrian surgery and adrenal insufficiency. I made the referral calls for both issues. I called endocrine, and we put the patient in the ICU because the patient tanked their sodium all the way down to 119, practically overnight.

It took three, maybe two and a half days for the endocrinologist of the hospital and for the intensive care specialist to actually accept my initial diagnosis. This is not because I am smarter, but simply because I happen to keep finding the same kind of predicament in these difficult patients, it's not very easy to make the call when the experience is there.

Today we did not dive into it in great detail, so I will mention hormones in passing. Chiari psuedotumor can be associated with empty sella. It is not necessarily a direct association, but rather, they can cause the empty sella since they increase the cerebrospinal fluid pressure; the convexity, the domelike appearance of the skull concentrates the pressure waves towards the base of the skull and there is a flattened effect on the sella. Sometimes, and this is not in all patients, we see hormonal dysfunctions follow.

The most common hormonal change we have found in these patients (by doing labs) was hypothyroidism. This type of hypothyroidism tended not to share the most telltale, classical signs that the endocrinologist would feel required to check off, but it was, in some selective cases, reacting well to supplementary therapy.

Then the second hormonal issue we find fairly often tends to be problems concerning LH and FSH. Besides their regular menses, which also complicate their headaches, some of these patients are frankly unable to conceive. Interestingly, within six months after surgery, many of them are actually able to conceive without any help.

The third problem we found concerned the adrenal hormone. Again, it was my ignorance that I did not know that EDS patients were more vulnerable for that kind of insult. I do not know what the mechanism is.

Then there are problems with behavior and cognition. Chiari "personality" is something that we have all experienced in our practice, but have never published. We are all familiar with patients who understandably— usually after years and years of being misdiagnosed or not listened to— develop this sort of sense of borderline paranoia, hyperattention to minimal things because they really do not know how to distinguish the proverbial forest from the tree in terms of their condition. So the patients will pay close attention to these floaters in their eyes with the same intensity they would to weakness in their lower extremities.

Because of this, the patients develop this kind of persistence and militancy in promoting their own clinical case or the clinical case of their fellow patients.

Brain fog is something that is described by patients; it is a terminology mostly used by the patient population. In more scientific terms, "brain fog" is expressed as the inability to multitask, inability to focus on specific tasks like mathematical problems and difficulty in retaining short-term memory.

Dr. Milhorat and I were discussing this phenomenon for a long period of time— we discussed it a lot, actually. We would say, "Okay, is this coming from CSF pressure, or is it faulty wiring?" Unfortunately, we really never discovered the answer.

Two or three years ago, I came across a very nice article with excellent pictures— the pictures struck me more than the writing. The article came out of India and used functional MRIs showing a probable wiring problem in people with Chiari I malformation who had these kind of cognitive issues.[5] The case numbers presented were very small, however, so perhaps the most outstanding part of the article were the pictures.

Depression is very frequently found in these patients. But, once again, for someone who is generally treated poorly by the medical community and diagnosed late, reactive depression is probably the best-suited explanation for these symptoms. ADD/ADHD is probably different because it is much higher than in the standard population.

And then there is the problem with autistic spectrum. I know where Dr. Henderson stands on this issue. Our position has been a little bit different after the initial enthusi-

asm. Our revised position being that Chiari I malformation was just a compounding factor of autistic clinical presentation.

For instance, if an autistic child gets pneumonia, the autistic symptoms worsen; when the pneumonia remedies, the autistic symptoms get better, too. A severely autistic child with symptomatic Chiari with headache behavior is, obviously, not going to say to you, "I have a subocciptal headache that is exacerbated by a Valsalva." However, if you do have a severely autistic child who also has symptomatic Chiari with headache behavior, removing the Chiari just removes one compounding thorn from that child's diagnosis. At that point, it does not rectify the autistic symptoms, but can provide higher functioning in that patient and allow that patient to be better managed long-term.

About half of us in this room were in Sydney for Dr. Stoodley's 2013 meeting on Syringomyelia. And I remember a boat ride back from the meeting site towards our hotel with Mr. Flint from the United Kingdom; and we're comparing notes about the different personalities associated with people who had Chiari and people who had Chiari and Syringomyelia. We were wondering aloud whether or not there was something different at the mechanical or pathophysiological level to explain those personalities.

We began noticing that people with Chiari, alone were having all these kind of ultra-attentive, almost neurotic personalities, while the people with Chiari and Syringomyelia, especially those patients that were the most sick, had this very stoic attitude. These patients were not neurotic at all. It was as if the two sub-populations were like two entirely different groups of people.

So we were wondering if there was some difference in the physiology to explain this. One of the ideas that Mr. Flint had, suggested that maybe some of the pressure was finding its way out of the brain and down into the syrinx. This pressure escape would suggest, therefore, that the brain was receiving less pounding while the syrinx formed. Obviously, this anecdote is more just a curiosity that I wanted to throw in.

Allergies bear noting, as well. Most of our patients have a lot of allergies to drugs, foods, and environmental agents. They tend to have an increasing number of allergies over their lifetime. Some of my patients have three or four medical alert bracelets because they cannot fit all their allergies on just one. We have patients with true food allergies and many other patients with food intolerances that, if corrected, actually cause a secondary improvement in the intensity of their symptoms, especially gluten. That is a lesson that I learned from Dr. Kula.

And recently – I am glad to see that Dr. Maitland is here – we found the compounding factor of mast cell. When discussing this, we get into another argument of the chicken or the egg: gut and brain. All of us have seen irritable bowel syndrome and opioid constipation in these patients; but, again, we have been educated just this morning from Dr. Henderson's input regarding the effect of the vagus nerve and dysautonomia.

There is more information about inflammatory changes in the GI wall, especially when somebody has food intolerance to gluten. There are also some neurotoxins which get released and, again, compound the effect of the Chiari I malformation on their symptoms whenever we see these patients with an abnormal gut.

To conclude all this rambling about the cervicomedullary area, it is not too surprising that a system with multiple interacting variables can generate several different scenarios. This area has all these packed centers. There are many cables in the cervicomedullary junction, many different forces. Therefore, there are different pathologies,

different pathophysiologic mechanisms from anterior, from posterior, from the side. Out of all these multiple possibilities, you're going to have some recurrent difference in areas, and there is not just one cookie-cutter presentation over and over.

But how many of these comorbidities are genetically linked? For example, the Chiari with EDS group seem to preset as a package, but, as was obvious from many of the observations this morning, many patients have mixed phenotypes. So it is not like a patient will walk through the door wearing a label that says, "I have a classic EDS without any confounders." Well, many of the patients with connective tissue disorders we see, when they come in, they will fill out the forms with a little bit of everything.

Another important point to make is that genetic testing is a long and winding road. If the genetics group I mentioned earlier out of Duke is any example, we can learn that very often you can spend time looking in the wrong direction. Their group researched a few particular chromosomes for three or four years, realized it was leading to a dead end and was forced to regroup and go in an entirely different direction. So for us to just expect that the geneticists are going to come up with the in's and out's of all this is wishful thinking on our part.

The geneticists will receive much more help when we as clinicians tell them about the observations we have made. In fact, the observation of Chiari and EDS having similar genetic phenotype to Klippel-Feil came originally from a clinical observation that Chiari and EDS sometimes present together. The geneticists chose to look at that, Klippel-Feil and connective tissue disorder and they actually got a hit.

Another point and question, the Chiari is perceived in the medical community as a kind of mixed salad bowl, in which some of the diagnoses are the true-blue classic Chiari I malformation with a small posterior fossa, tonsillar herniation, and cerebrospinal fluid blockage, et cetera; but others are not really true Chiari malformations, but rather they are Chiari-like or Chiari plus something else.

So then what kind of salad is in the bowl of the cervicomedullary syndrome? As we see, if Chiari is already complicated, the cervicomedullary syndrome will then open a much larger Pandora's box.

Some other considerations largely follow common sense. For instance, encountering patterns requires a full immersion through large patient numbers. You cannot find any clinical pattern if you see only ten patients per year. Additionally, identifying those patterns require you to keep your eyes open for them; understanding the patterns is easier when a close-knit team is involved and works together well.

I have been extremely lucky in my career. When in Italy, I was trained by the renowned Prof. Victor Fasano. When I came to the States, I was trained and then had the honor to work with Dr. Milhorat, Dr. Kula, Dr. Nishikawa, and then Dr. Rekate.

I was always the dumbest guy in the room. It was really a blessing to see and hear all these people pose the problem from different perspectives. It was wonderful to always have educated, stimulating and sometimes rather animated conversations about these topics. It was a blessing just living and breathing this kind of problem, 24/7.

I stole and I imitated many of these thinking patterns over the years. That has been, for me, a blessing. So I am sure that in the future, if we want to find more patterns concerning these kinds of problems, we should have to have a similar approach of discussion and stimulation. It helped me; it probably is going to help others.

The other downside is that very often some of these patients who are more problematic will be swept under the carpet by clinicians who know less, who are less informed or who simply choose to look the other way. Very often when we receive patients who have had previous surgeries, they will have the same litany: “I was treated by my doctor, I went back to my doctor and my doctor said that I am cured and that I should go away; but if I am cured, why do I have the same symptoms that I had before the surgery?” So obviously, if a bunch of patients are having this problem and we do not know how many since they are often swept under the rug, these patterns are likely going to be underdetected, underrepresented, and misunderstood.

Another problem is the *ipse dixit*. The Western scientific thinking has been heavily affected this *ipse dixit*, something Aristotle quoted in his generation in 400 AD and that had continued on until about the 16th century. There was a long gap and a long line of people who were just deferring upwards and saying, "That guy said it; therefore, I am not going to mess with it."

Instead of this constant deference, sometimes we have to look at all the facts and have to have the courage to say that something does not fit. Most of the observations that I have listed so far date back to just about ten years— and too many times to The Chiari Institute.

To this date, besides this group, most of the people dealing with Chiari in this nation and somewhere else either choose to not see these patterns or if they already have been informed about it, they for some reason refuse to see the patterns.

The question is: What are we not seeing? In all these patterns, what are we not seeing in the relationships among the pathologies? What are the patterns that we are simply blind to? What are we misunderstanding? What if, so far, we have just been patting each other on the back to convince ourselves that what we are doing so far is great and we can just blindly build on that? Maybe some of the things we are doing are, frankly, wrong and maybe we are going to have to realize it ten years from now.

I think that the best lesson that I have had so far came from watching Dr. Milhorat deal with failures. Whenever he was having a patient who was a surgical or a clinical failure, first of all, he was getting physically sick over it. I remember, some, he was losing sleeping about it; he would reiterate the case over and over and over.

I have a kind of silly story, but it will give you a better idea of the man. There was a patient that we could not fix and we were at the Long Island College Hospital in the first Chiari center. Dr. Milhorat calls me, puts me in front of the MRI that I knew very well and tells me the story that I knew very well. Then the door opens, and there is the senior attending in the place comes in. "Oh, come here, come here, Rick." And he starts the story over again, with me at his side. The same process continued after a few people walked in. Four hours and a half later, the guy sweeping the room came in. His name was Jose. And Jose, two minutes later, was next to Dr. Milhorat in front of the MRI. Dr. Milhorat was trying to explain to Jose what we have done so far. So obviously, Dr. Milhorat was stressed about this patient and felt he had to talk to as many people as possible.

But because of that patient, we learned so many more things about what we should and should not do in a reoperation. Learning from that patient, we improved practically overnight in our ability to contain cerebrospinal fluid leakages.

So the issue is failures. If we have patients who do not fit the mold, patients to whom we have given our best and could not help, probably those are the patients that will be the key for us to understanding what we either are not seeing or are misunderstanding.

Thank you very much.

Discussion following presentation

DR. CLAIR FRANCOMANO: I just wanted to make a comment about the endocrine issues because I spent last weekend at the American Academy of Pain Management meeting in Washington, D.C.; and there was an internist there by the name of Forest Tennant, who was talking about endocrine consequences of chronic pain.

The patterns he has observed in the chronic pain patients really parallel with what we see in a lot of these patients with Chiari and hereditary connective tissue disorders. So I wonder if it is a more common mechanism not specific to these patients but something that is typical to chronic pain.

One very, very interesting comment that he made was he has had something on the order of 20 patients with Ehlers-Danlos syndrome and chronic pain who have responded really well to oxytocin. So that was kind of an interesting anecdote.

DR. PAOLO BOLOGNESE: What do you think is the mechanism behind it?

DR. FRANCOMANO: Well, his hypothesis is that the stress of chronic pain then stresses the adrenals; and that in the initial stages of the chronic pain, you get increased adrenal output, and then eventually, over time, diminished adrenal output.

I do not know the connection to the pituitary. But there definitely were, in his experience, decreases in FSH and LH.

DR. BOLOGNESE: On the other hand, a lot of other people have seen stress in the hypothalamic-hypophyseal axis. So it is kind of difficult at that point to determine at which point in the cascade do we see the common final pathway what is cause and what is effect.

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3. Craniocervical Junction Abnormalities: Beyond Chiari Malformation in Dogs

DR. CURTIS W. DEWEY, DVM, MS

I am going to switch gears a little bit and talk about dogs. I will talk a little bit about humans, just as a comparison. I know that Dr. Marino has spoken to you about Chiari in dogs before, or rather Chiari-like malformation, which is terminology that was decided on some years ago. I never really liked it – it seems very noncommittal to me, but I was not there to vote on it. In any event, you will hear me say Chiari or Chiari-like throughout the presentation, but I will mention some other issues as well. Of note, Chiari-like malformation is mainly found in little dogs, Cavalier King Charles Spaniels being the most common breed to have this observed. It is similar to Chiari Type I in humans, and is often associated with Syringomyelia.

There are medical and surgical therapy options. Some of us were discussing a little bit over dinner last night and you may find this a little strange, but there is actually a little subgroup of veterinarians who are neurologists who think this is not a surgical disease. Yes, I know – strange. I think this notion is contraindicated always. Always and never usually do not work out very well together.

You have probably already seen this, but I am going to go over really quickly what we did with the Chiari Institute. We started doing foramen magnum decompressions and at times there was a fairly high relapse rate. So we met with Dorothy Poppe, Dr. Milhorat and Dr. Bolognese to come up with this procedure already being used in humans – the only difference for us is that the hole we deal with is smaller in dogs. The procedure is successful in most cases and it is a long-term success, as well – if we have time, I will explain what that means. It is kind of controversial in veterinary medicine – not to me, but I suppose to other people, it is controversial. There is a very large data set at Long Island Veterinary Services (LIVS). We have some cases at Cornell to add to that dataset, but private practices tend to have a higher case-load than we do at a university.

Very quickly, what does Chiari-like mean? Frankly, I do not know – to me, it is kind of confusing. One thing we have found, though, was that when this was first described in dogs, it subsided a little bit, but there was a rush to publish on it. We found out, I think fairly recently, that a lot of the issues that people were calling Chiari, Chiari-like or what have you, were actually craniocervical junction abnormalities that were not really Chiari. They saw something was pinched in the area, and they quickly lumped it in a large group and called it a Chiari. So that group is what I am going to focus on in this talk; there are multiple other disorders that have become evident and even more terms have since come out, which can get kind of confusing.

Instead, I like to refer to this as the craniocervical junction abnormality group because once you say that, you can describe something more detailed to the individual patient. Basiocciput, foramen magnum, atlas and C2: these are the structures I tend to think about when I consider this area – probably not very different than all of you. The embryonic development is complicated, but kind of boring so I will not get into it; but

when mistakes happen during development, it should not be a big surprise that sometimes there are more than one mistake. And we do have some examples where there is more than one abnormality in this region.

I have read the human neurological literature and while you do not always use the same terminology, "craniocervical junction abnormalities" seems to be used as an umbrella term, which is then subdivided to represent different issues. This makes a lot more sense than trying to be too specific, at once. Some of these subheadings are occipital, atlas, and axis malformations. This is an example of atlantooccipial overlap (AOO), which would be similar to basilar invagination, cranial settling. (**Fig 1**)

We are going to discuss Chiari I malformation, atlanto-axial (AA) instability, AOO, and atlanto-axial divot, which I will get to in a little bit. We see issues like AA instability in dogs even smaller than the Cavaliers – the toy group. Occasionally, we will see this in bigger dogs but not as often. Chiari-like malformation is analogous to Chiari I in humans.

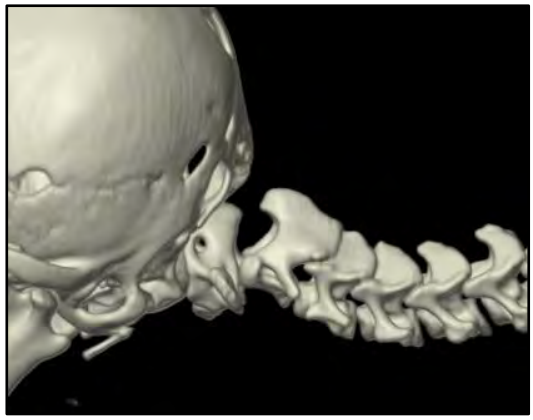

Figure 1

If we see C1-C2 instability, that instability tends to just be called AA instability or subluxation. To me, it is luxated, not so much subluxated; but I have wondered if some of these may actually be some type of basilar invagination involving the C2 vertebra, not the typical atlanto-occipital subluxation.

Because of all this, the new terminology makes inherent sense and it underscores the variety of possible disorders that we will see with this. This is an example of a dog with a lot of those various issues. (**Fig 2**) Just below (a), we can see C1, C2 below that; and that small indentation below (d) made of connective tissue is the atlanto-axial divot I had mentioned earlier. This image is from a Pomeranian-type dog.

The complexity shown in the new terminology and even just this image helps emphasize the need for complete imaging studies in these cases. Since recognizing that these are not all Chiari-like malformations, we have noticed that we are sometimes unable to discern what is bone versus connective tissue in these dogs. To address this, we do an MRI to show us what is wrong and to get a nice soft tissue detail; and then we do a CT through the identified abnormal region to really find out what is going on in those bony structures. I also use the CT to measure when I put implants in.

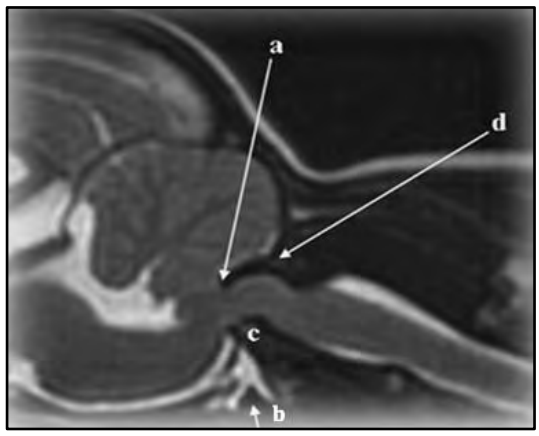

Figure 2

One last note about this new terminology and subheadings: they have really helped us individualize our surgical plans to each patient. Here is an example of a young Akita. (**Fig 3**) What the heck is that? We know it is a craniocervical junction abnormality. If I had to give it a specific name, I may call it occipitoatlantoaxial malformation. The abnormality was asymmetric, C1 was a very small, almost nubby-looking thing, and C2 was articulating with the occiput on one side but not the other. Although this was complex and something unique to this patient, the overall umbrella terminology of "craniocervical junction abnormality" helped us better handle this patient.

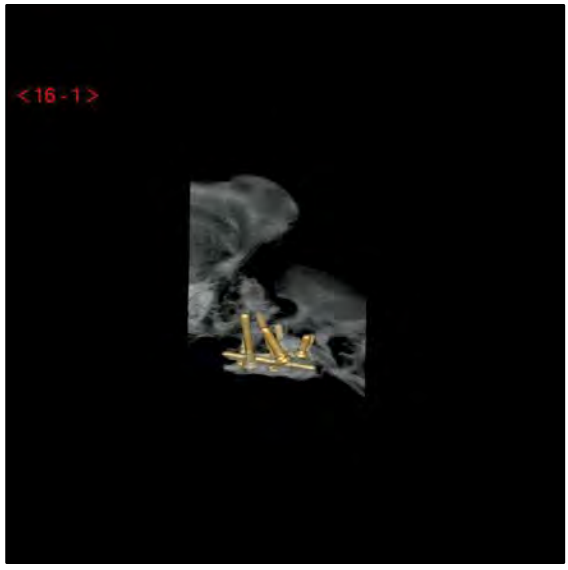

Figure 3

Briefly, I want to discuss neuropathic pain. I know a little about what has been done in people, but dogs, obviously, have other treatment plans. I had been using a lot of Lyrica instead of gabapentin; to me, it seems to work longer and last longer, at least in dogs. Gabapentin's half-life is three or four hours in a dog; the half-life of Lyrica is seven hours and it seems to be a stronger drug. I have also noticed that there are a handful of dogs who seem to stop responding to gabapentin; I would put those dogs on pregabalin and they would improve. It also seems to have a more potent effect on the targeted calcium channel. This is not the dosage that you will be using, but we use 2 mg/kg per day. Usually, if you use and maintain this dose, it will work for neuropathic pain. For epilepsy, you have to go higher. I learned the hard way, however, that for epilepsy you will have to start at the low dose and work your way up, or the dog will get really sedated. Because a lot of the drugs will say that and it is not really true, we prescribed an initial 3 or 4 mg/kg during a clinical trial for epilepsy and the owners were upset with me because their dogs were asleep. So it is best to start at 2 mg/kg and work your way up if you ever plan on treating a dog.

Figure 4a

This is Skiddie. (**Fig 4a**) He is cute, right? Well, he was mean. He was also in a lot of pain so maybe those things were related. My impression was that the pain was cervical, and it is just my impression because it was very difficult to examine him to be sure. If you tried to touch him, he would try to bite you – and he had pretty good aim. He also experienced screaming episodes throughout the day.

Because he was neck-guarding, we were pretty sure it was his neck. It turned out that he had a syrinx over C3 and another one over his cranial-thoracic spine. He had some flattening of the cerebellum and a little bit

of an overlap of his dorsal arch of C1 and the dorsal aspect of his foramen magnum. (**Fig 4b**) This is an axial CT view. (**Fig 4c**)

With Skiddie, we had some pretty good evidence that C1 was moving around, so we thought he had a sort of Chiari and maybe basilar invagination. I did not want to just do a foramen magnum decompression and just leave it at that, letting things potentially move around. It was interesting to hear today from whoever it was that talked about it, that I could actually destabilize the area more by treating it as a Chiari, alone.

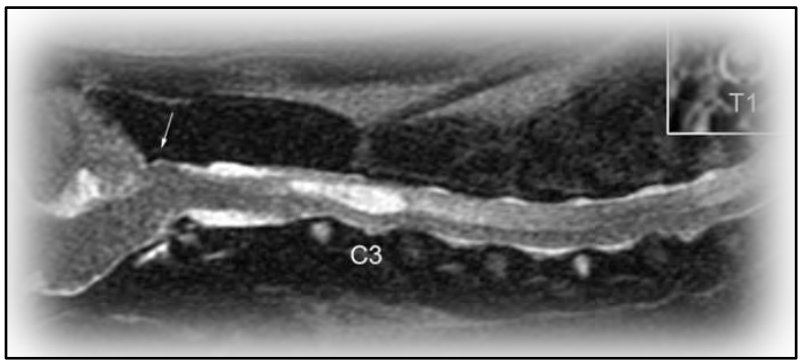

Figure 4b

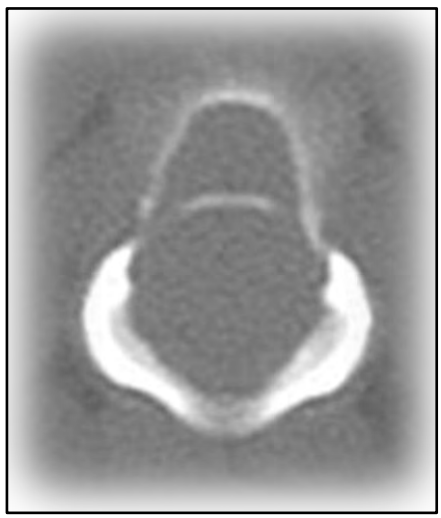

Figure 4c

So, for Skiddie, I did a foramen magnum decompression, put on a plate, and also put some pins and screws in between the occiput and C1 to stabilize it. It was sort of a cranio/laminoplasty.

Atlantooccipital overlapping in dogs is probably a variant of basilar invagination or impression in people. Dogs do not experience as much cranial settling because they are quadrupeds.

There are varying levels of severity. I have had some dogs come in that were absolutely normal, had some minor trauma and were having neck pain and maybe some difficulty walking who resolved without needing surgery. This is all challenging partly because of where this is and how small these abnormalities are. The arch of C1 in these dogs (often Yorkies, Pomeranians, Brussels Griffon) is probably only about 2 to 3 millimeters thick.

In people, you see a lot of cranial settling. There are some similar issues in dogs. These can occur as an isolated disorder or in conjunction with other things. It has been described as a "telescoping" of C1 and/or C2 towards and into the foramen magnum. As I mentioned, I have seen dogs that, by veterinary terms, would have AA instability, but they also have C1 going into the foramen magnum.

Basilar invagination could be static of dynamic. Stabilization is often necessary—it is relevant to mention that there is more "stuff" to fasten to in people than in dogs for these kinds of surgeries.

This is another example of a dog with some craniocervical junction problems. This is a five-month-old female English bulldog named Giblet who had non-ambulatory tetraparesis, progressive over several weeks. (**Fig 5a**) We gave her steroids and she was able to walk on prednisone, but not very well – it was easy to tell that she had an ataxic gait in all four limbs and she tended to fall over. She also had some neck pain on palpa-

tion and also some TL pain on palpation, which we never really found anything image-wise. She did not have a syrinx there, but all in all, everything seemed to point to the craniocervical junction.

So what did we do with Giblet? First, we imaged her and came up with this image on her MRI. (**Fig 5b**) What do you think? It does not really look that good. I have seen a couple different variant of this. Sometimes that compression at C1-C2 ends up being all bone, and sometimes it is a little bit of bone and some connective tissue. Giblet's was a little bit of bone but a lot of connective tissue. Also, if you look ventrally at this image, you are not able to see much of a dens on Giblet. The space between C1 and C2, ventrally, looks pretty large for a dog, too; it is a little widened. I was concerned, then, that Giblet has some AA instability, as well as that divot.

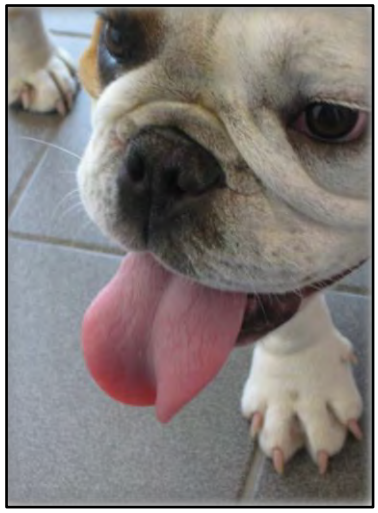

Figure 5a

We looked at the CT in different positions and it did appear that things were moving around. It looked as if there may have been a little remnant or an improperly-formed dens, allowing for movement.

The dilemma we encountered was that since there was not a lot of bone stock dorsally and it was already under compression, most neurologists, most surgeons, do not like doing dorsal stabilizations for AA instability. There is not a lot of bone, period, but there is must more ventrally. For most people it is a concern.

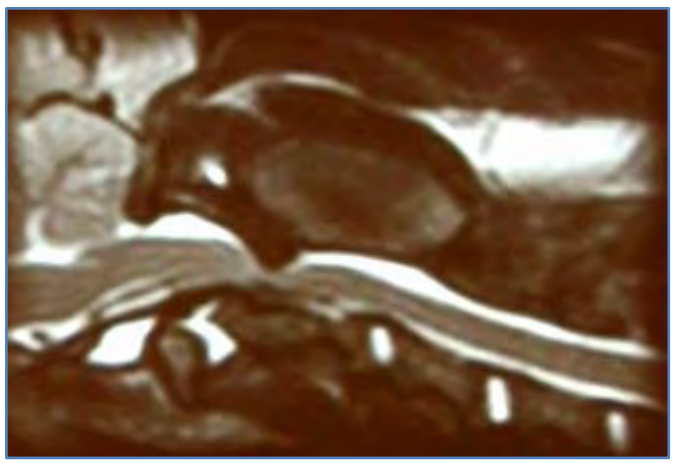

Figure 5b

I prefer ventral stabilization; but, obviously, that is not going to get rid of that big giant wad of whatever that is pushing on Giblet's spinal cord. As such, I really thought we needed to do a large dorsal decompression. So we decided to do something fancy – at least, I thought it was fancy at the time. We did a ventral stabilization and dorsal decompression with added stabilization. I just put some screws in there too while I was in the neighborhood. That divot was actually firmly adherent to the dura, so I had to take the dura off in that section.

Post-operatively and now off-steroids, Giblet was able to walk normally with a visible difference. The owners were so happy with Giblet's recovery that they rewarded her by feeding her a lot more food – so now she is fat. We actually had to give them some dietary advice and not overfeed her like that.

This atlantoaxial dorsal divot might be a combination of basilar invagination— we are not really sure – fibrous connective tissue sometimes with some bone between C1 and C2 and occasionally as I said, bony. We think there is probably some instability component to it, maybe a little bit of a congenital anomaly there. It often does go along with Chiari-like malformation in dogs. Sometimes it is very small and we kind of ignore it; and other times it is bigger and it will be observed with AA instability.

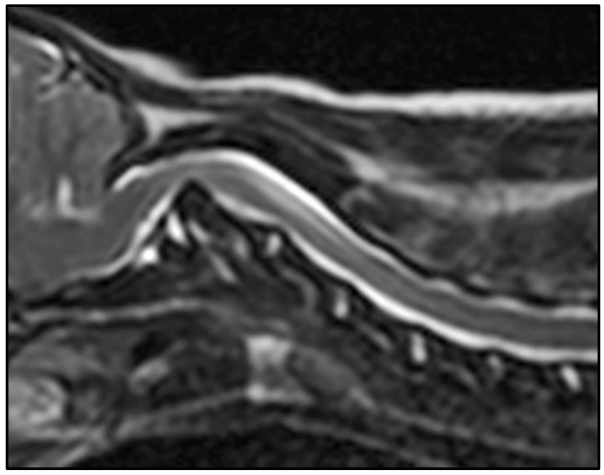

Figure 6a

Gracie is a seven-month-old female Yorkshire terrier, who weighed about 2.2 pounds. Acute onset and rapid progression of tetraparesis, progression to non-ambulatory status over several days, neck pain. Gracie could not move her legs.

Here are Gracie's MRI (**Fig 6a**) and CT (**Fig 6b**). Severe displacement of C2 in relation to C1, severe compression of the spinal cord. That is typical AA instability. We often see it in toy miniature breeds, usually young, less than two years of age. We do see it sometimes in older dogs. Sometimes, we will have a dog who has what you would not consider a traumatic event but rather a minor trauma – jumping on the bed, playing too roughly with another dog, that sort of thing. It is a congenital absence of the dens, sometimes absence of ligaments that are supposed to hold the dens in place. It can be acute or gradual, it may wax and wane. They usually have obvious neck pain and cervical myelopathy of varying severity.

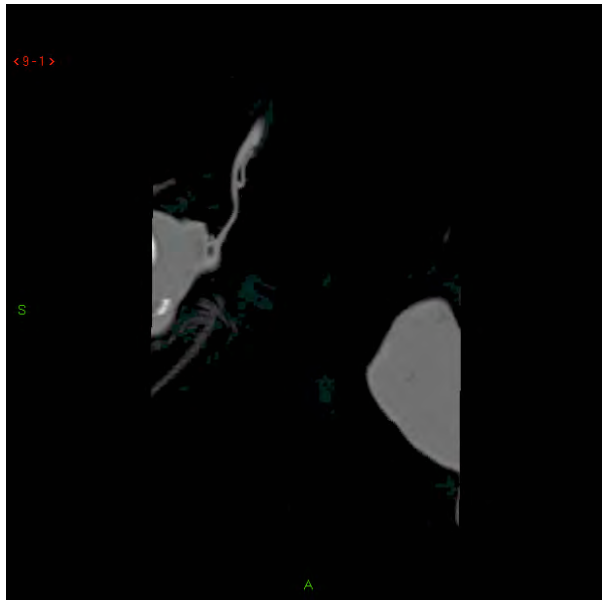

Figure 6b

Squeaker was a pretty stoic little Pekinese; but you could tell that he obviously did not want to move his neck. If you palpated this dog, he would kind of look at you as if to tell you not to do that, even though he would not yell or anything. So I was convinced he had some neck pain because he kept his neck extremely still. He had good sensation, but no motor.

Regarding the treatment of this disorder, there also is some controversy in dogs, though not as much. I think some people will treat this medically and conservatively with confinement therapy – they will put a brace on.

I do not believe in the braces. I think the lever, the pivot point, is too close to the nose. I think what happens when you put these splint things on these tiny dogs, the animals are unable to move because the braces are so heavy for their little bodies. They also tend to get dermatitis. When someone will realize that the brace is not working and they elect to do surgery, suddenly, they are faced with a skin infection. So I do not generally like that. It has been found that the success rate of medical management, braces, confinement may be about 65 percent. The other percentage usually does not survive because they cannot breathe or their heart stops. So compared to the surgical success rate, which can be somewhere between 85 percent to close to 100 percent, I do not think that is worth the risk. So I prefer to do surgery with this and, as I said, I tend to go ventrally versus dorsally.

There are a handful of surgical complications. Intraoperative/perioperative death: the surgery is close to the medulla and there is also sympathetic flow going through there. Other issues include worsening neurologic status, implant migration (usually manageable), and fixation failure. Fixation failure is related to implant migration but it is not really a problem once it has been fused.

Post-operative care is important. You treat them like their heads may fall off because that is kind of what is going to happen. I confine them for about eight weeks, very limited activity. Regarding splints: I do not like them nor believe in them. If they are very difficult to keep still, then I just use sedation. In these dogs, post-operative pain does not tend to last very long. I have also started doing electroacupuncture in addition to their fentanyl and other narcotics. They tend to recover very quickly as far as their pain. Depending on their neurologic status beforehand, that will go along with how quickly they get their ambulatory status back. Their prognosis is pretty good. My dogs typically do fine. I cannot remember the last one that did not; but if you look at all of the surgical literature, it is more than an 80 percent success.

Post-surgery, Gracie did really well. Probably about two months after surgery, she was walking again. So the length of clinical signs and neurologic severity pre-op have been inversely related to outcome by which I mean I have had quite a few of them that have been down for a while and they seem to do well—they just might take a little longer to get up.

Any questions?

Discussion following presentation

DR. TODD BELL: Thank you. Very interesting. In the human population, there seems to be a gender predilection in symptomatology. Do you see that in dogs, as well? And if so, does it vary based on whether the animal is spayed or neutered?

DR. CURTIS DEWEY: There does not seem to be a gender predilection. I have not seen it nor have I read anything about spaying or neutering. One of the problems is that a lot of these dogs will come in with the problem before they are at an age that they are going to be spayed or neutered. So it would probably interfere with the statistics because I think most veterinarians spay/neuter around six months.

DR. ROGER KULA: What percentage of the dogs have Syringomyelia? Is it similar to the human population? Ten or 15 percent maybe?

DR. DEWEY: Nobody knows that. That really has not been looked at. So the question is—I am assuming you are talking about AA instability in dogs?

DR. KULA: Yes.

DR. DEWEY: Yes, so no one has done that. One of the problem that I have noticed is that some of them will have a syrinx.

One of the problems is that a lot of these dogs will go to surgery based on radiographs. That is actually in some of the textbooks claiming it to be "classic". So they may have a syrinx, but we just do not see it because no one has investigated this issue. In AA dogs, I actually advocate an MRI partly because they ask for it, but also partly because sometimes they may have other problems. So if your AA dog is not doing well, it might be because you did not fix all the diseases.

DR. KULA: If they have a syrinx that collapses, when you correct the constriction or the deformity, do you have any experience with shunting any of the syrinxes in the dogs?

DR. DEWEY: No. Dr. Marino and I have talked about shunting syrinxes, but we have not done it yet. He can tell you about some of the cases at Long Island Veterinary Services where he has re-imaged the patients and the syrinx had shrunken somewhat. Someone has done it, but it is a very small case series; and it is kind of hard to tell how they did. The results were described in vague terms and I believe it was only 12 dogs.

DR. KULA: Any other animal species like cats, kangaroos, whatever else with similar deformity?

DR. DEWEY: Yes, but not very commonly or they will not commonly be presented. Cats do not tend to get AA instability. Sometimes bigger dogs will have it. Importantly, trauma is different.

I did one miniature horse—the smallest miniature horse in the world is what I was told. It had a congenital abnormality that seemed like he had an absence of the dens. It actually was easier to perform the surgery because it was a horse, like a really big Great Dane.

As far as Chiari-like malformations, there have been a few cats – mainly the smushy-faced Persian exotic short-hair cats. And there have been some reports in the wildlife group of lions with Chiari malformation.

But as far as congenital AA, I have seen one miniature horse and no cats. As far as trauma is concerned: it still happens mainly in dogs, they get into trouble more often than cats. I also had one deer that needed AA surgery.

DR. SUNIL PATEL: How do you position these dogs?

DR. CURTIS DEWEY: For the AA surgery, they are positioned in dorsal recumbency and just slightly extend their head. So we position them that way, make sure they are midline.

Then, so they are not moving around, because if you get off the midline it can get a bit frustrating especially considering how small they are, I will take some white tape and tape them over their canines to gently strap it down so they are not moving before we put little pads around their neck.

I will also take a skin staple, sterile staple device once they are shaved and I will feel C1, the back of C1; just off midline, I will then put a little staple. It is not the best localizer because the skin moves around, but it is pretty good because sometimes, especially in tiny dogs, you have trouble identifying vertebrae. And usually, if you got that, you can find it pretty quickly. I like to cut down time as much as I can because these dogs tend to get hypothermic. They are tiny and once they get below 90 degrees, you have to move faster.

AUDIENCE COMMENT: Generally speaking, these patients are one to two pounds? For most cases in veterinarian medicine, you do not have intra-op fluoro you do not have intra-op CT? You have fluoro, you just do not have it in the OR. So a lot of this is done by feel. You have radiographs, MRIs.

DR. PAOLO BOLOGNESE: What kind of instrumentation do you use?

DR. DEWEY: It depends. One puppy was just five weeks old, and I figured his bones would be pretty soft. I used Synthes and a company called MedArt. You probably know all this. They make these titanium screws that are 1.5 and 2.0 millimeters and that come in a set. It has a little handle and detachable screwdriver and a detachable drill bit. So instead of using a minidriver or something like that to put it in, you can actually take this little thing, make your hole and then put the screw in. Usually, I will use something like a minidriver.

4. Joint Hypermobility Syndromes: Epidemiology and Neurologic Implications

DR. CLAIR A. FRANCOMANO, MD

It's really a great pleasure to be with all of you. I learn so much from these meetings, and I appreciate the opportunity to participate.

Fraser asked me to talk about the epidemiology of the joint hypermobility syndromes. Unfortunately, there isn't really that much information out there on this subject. This, I think, is one of the great gaps in our knowledge and something that we all can think about in trying to improve as we're going along and designing these studies that we're thinking about.

When you look at joint hypermobility, it is seen as a feature in over 140 of the clinical syndromes that are listed in Online Mendelian Inheritance in mankind. The Online Mendelian Inheritance in Man is a compendium of human genes and genetic disorders, started by Dr. Victor McKusick at Johns Hopkins. It is now under the auspices of Dr. Ada Hamosh at Johns Hopkins, and is a comprehensive annotative bibliography of the medical genetics literature.[1]

Joint hypermobility occurs in congenital anomaly syndromes, the short stature syndromes and in the hereditary disorders of connective tissue. Some experts lump the short stature syndromes in with the hereditary disorders of connective tissue and consider them under one big umbrella of connective tissue disorders. It depends whether you're a lumper, or a splitter.

We think about the connective tissue as the supporting and protecting elements of the body, including the bones and cartilage, tendons and ligaments, the collagen fibers, the elastin fibers, and mucopolysaccharides. Though we think of the connective tissue as a scaffold, it also plays a really key role in signaling. For example, in Marfan syndrome, the genetic mutation is in fibrillin, which is a structural protein. The work of Dr. Hal Dietz and his colleagues at Hopkins, has demonstrated the important effect of fibrillin on TGF beta signaling by which many of the manifestations of Marfan syndrome occur.

The most common of the hereditary disorders of connective tissue -- not including the skeletal dysplasias -- are Marfan syndrome, Loeys-Dietz, Stickler, osteogenesis imperfecta, and the Ehlers-Danlos syndromes. The following is a brief run-through of the physical findings that we look for when we're making the differential diagnosis.

In Marfan syndrome we see tall thin stature with relatively long arms and legs; scoliosis; pectus deformity; arachnodactyly (long fingers and toes) and dolichostenomelia. Aneurysmal dilatation of the ascending aorta may lead to dissection and rupture; and there may be dislocation of the ocular lenses.

The thumb sign: a person is able to put the thumb across the palm of the hand, and close the fingers over it, such that the thumb will stick through. This is a useful test when looking for arachnodactyly.

Loeys-Dietz syndrome was recognized only a few years ago by Hal Dietz and his postdoctoral fellow at the time, Bart Loeys. These patients have aortic dilation similar to what we see in Marfan syndrome. However, their blood vessels exhibit significant tortuosity, which is not seen in Marfan syndrome. Craniofacial features in of the Loeys-Dietz syndrome include hypertelorism, malar hypoplasia, and either a frank cleft palate or a bifid uvula. The tortuosity of the blood vessels and the hypertelorism that is typical of this disorder. This illustration, from one of the papers initially describing this entity, shows the bifid uvula (**Fig 1**). Since recognition of the bifid uvula in Loeys-Dietz syndrome, we geneticists have all become "uvulologists" because that is one of the things that we really look for in our clinical exam.

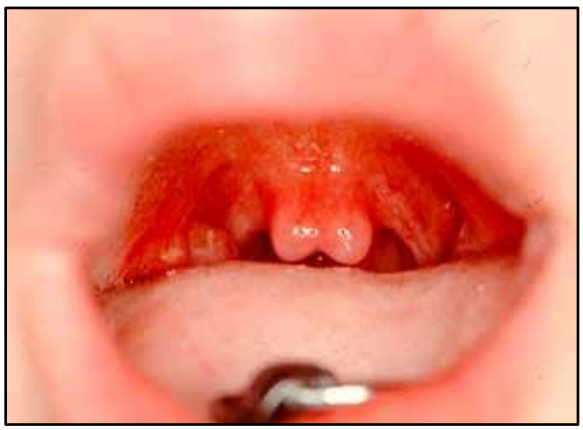

Figure 1 - Bifid uvula; seen in Loeys-Dietz and Stickler syndromes

In Stickler syndrome there is sensorineural hearing loss and vitreo-retinal degeneration, which may lead to retinal detachments. In its worst form this can lead to deaf-blindness. Affected persons also have premature osteoarthritis, and there may be cleft palate or bifid uvula, Pierre Robin anomaly with a small chin, which can be associated with the cleft palate. And radiographically these patients have a very typical spondylo-epiphyseal dysplasia. The radiographic changes that are typical for this condition that involve changes both in the spine with flattening of the vertebrae and also epiphyseal dysplasia. This photograph illustrates the epiphyseal disruption in the hips (**Fig 2**).

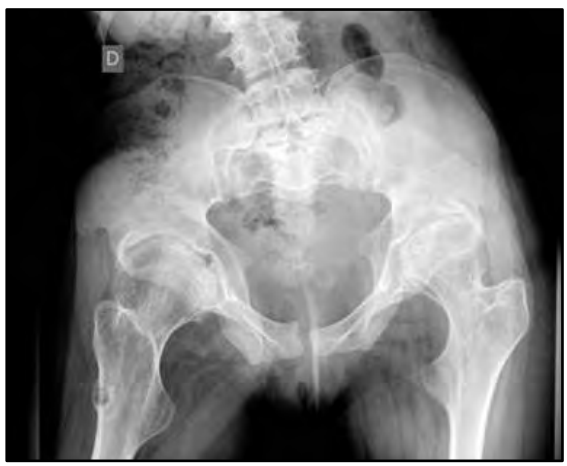

Figure 2 - Epiphyseal dysplasia of the femoral head in Stickler Syndrome

Osteogenesis imperfecta is also known as brittle bone disease, and there are four major types. And two of these are actually associated with average stature. So you don't necessarily have to have short stature to have the osteogenesis imperfecta diagnosis. Frequent fractures are the hallmark of this disease. Affected persons may have blue sclerae; dentinogenesis imperfecta; hearing loss; and wormian bones on x-ray examination of the skull, which can be a diagnostic feature. This figure shows wormian bones in the skull (**Fig 3**). You may also see blue sclerae

Figure 3 – Wormian bones as seen in Osteogenesis Imperfecta

(**Fig 4**), and dentinogenesis imperfecta, or poorly formed teeth with dysplasia of the dentin.

The Ehlers-Danlos syndromes – of which there are three major types – the classical type, the hypermobile type, and the vascular type - all exhibit joint hypermobility. In the vascular type, there may be aneurysmal dilatation and rupture of the medium-sized arteries, most often in the abdominal cavity. So that would be the splenic artery, the hepatic artery, and the gastric artery. There may also be rupture of the carotids and the femoral artery in this disorder. And sometimes you will see aortic dilatation and rupture. There may also be rupture of hollow organs, including the bowel, bladder, and uterus; so pregnancy can be extremely dangerous to woman with this disorder.

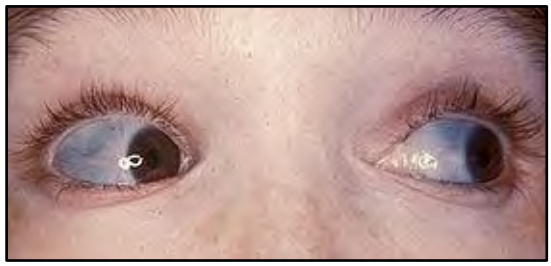

Figure 4 – Blue sclerae as seen in Osteogenesis Imperfecta

In the classical type, there is extremely stretchy skin, which is fragile and translucent and will frequently tear with minimal trauma. Figure 5 illustrates the very stretchy skin typical of the classical type. (**Fig 5**)

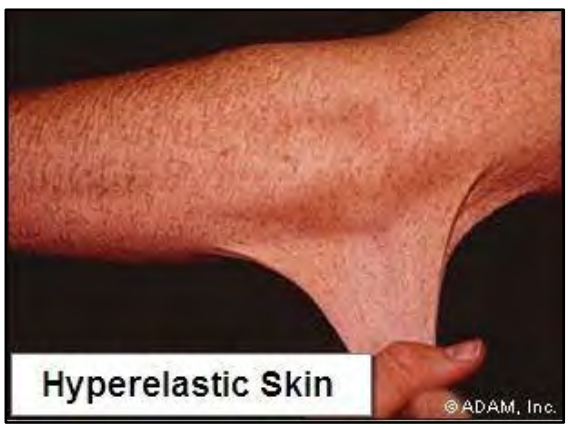

Figure 5 - Hyperelastic skin as seen in classical Ehlers-Danlos syndrome

The hypermobile type is exemplified by joint hypermobility but less severe skin involvement. We use a scale called the Beighton scale, which is a nine-point scale to measure joint hypermobility, to assess for hypermobile joints. (**Fig 6**) Other joints, such as the hips and shoulders, may also be unusually flexible, as will the small joints of the hands. You'll often see patients wearing ring splints to stabilize the small joints of their hands. The nine-point scale, I believe, is a very useful scale; and we discussed this yesterday when we were talking about screening for hereditary connective tissue disorders in the CDEs that we're putting together.

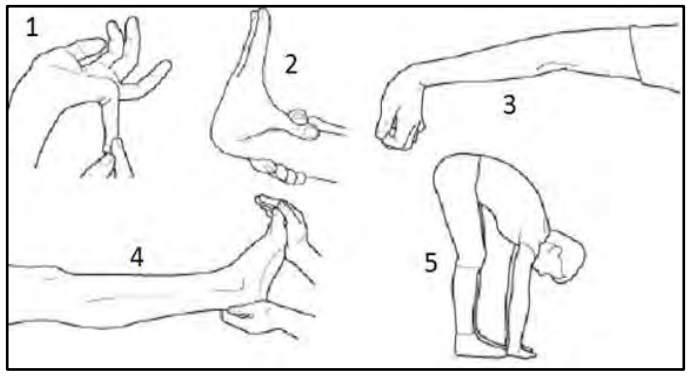

Figure 6 - Beighton scale for joint hypermobility: (1.) 5th finger hyperextends beyond 90 degrees (2 possible points) (2.) Thumb touches forearms (2 possible points) (3.) Elbow hyperextends beyond 190 degrees (2 possible points) (4.) Knee hyperextends beyond 190 degrees (2 possible points) (5.) Able to put palms on floor without bending knees (1 point)

Measuring stature and body proportions can help point to Marfan syndrome if a patient very tall, and has relatively long arms and legs. We always do an echocardiogram because the aortic root will be dilated often in Marfan syndrome and also in Loeys-Dietz syndrome.

An ophthalmology exam can help us distinguish between Marfan with the dislocated lenses, and Stickler syndrome with the vitreoretinal degeneration. An ophthalmologist also will likely make a comment about the sclerae.

Audiology is important to determine the sensorineural hearing loss that we see in Stickler syndrome. Sensorineural loss also in osteogenesis imperfecta.

The family history is very important. Was there anybody in the family who died suddenly and unexpectedly? That points to one of the aneurysmal dilatation syndromes. Was there a cleft palate? That will point you to Stickler syndrome or Loeys-Dietz. Premature osteoarthritis suggests Stickler syndrome and the frequent fractures are most often seen in OI.

The complications of the joint hypermobility are many. We see chronic musculoskeletal pain from muscle spasm and myofascial trigger points. There's neuropathic pain from many different causes, including degenerative disc disease, spondyloarthropathy, craniocervical, atlanto-axial and cervical instability, as well as nerve impingement at lax joints.

There are also complications of the cervical instability and co-morbid neurologic conditions, including cervical myelopathy, Chiari malformation, tethered cord, autonomic dysfunction and headache, and CSF possibly resulting from dural ectasia.

So what do we know about the prevalence of these conditions? The information in the current medical literature is presented in the Genetics Home Reference published by the National Library of Medicine[2]. The prevalence of all types of Ehlers-Danlos syndrome combined is estimated at 1 in 5,000.[3] I think those of us who are looking for these patients and see them frequently would estimate that the hypermobile type is actually much more prevalent than that. So some good epidemiologic studies in the modern age, using current diagnostic criteria, would be very helpful. Marfan syndrome is estimated at the same frequency (1: 5,000).[4]

The literature says Stickler syndrome is between 1 in 7,500 and 1 in 9,000 persons[5]; and OI, between 6 and 7 in 100,000.[6] There are no epidemiologic features out there on Loeys-Dietz syndrome, because it was recognized as an entity so recently.

Dr. Marco Castori, who is a geneticist in Italy, has written extensively about joint hypermobility, joint hypermobility syndrome, and Ehlers-Danlos syndrome.[7,8] He has proposed two different hypotheses about whether Joint Hypermobility is a bridging phenotype that unites these various hereditary disorders of connective tissue, or that joint hypermobility exists as a separate entity.[9] I favor this second hypothesis, that Joint Hypermobility/Hypermobile type of EDS exists as a separate entity. We know, for example, that the classical type of Ehlers-Danlos syndrome, results from specific gene mutations; the type V collagen genes, which distinguished EDS-Classical from other hereditary disorders of connective tissue. And the vascular type of Ehlers-Danlos syndrome is caused by mutations in type III collagen, again a very distinct entity.

However, for the hypermobile type of Ehlers-Danlos syndrome, we have not yet identified a gene mutation. So this still remains in need of molecular verification and validation. A lot of people are working hard on that; and when we have the molecular

answer to that question, I think we'll be able to do better epidemiological studies by looking for alterations in the identified gene or genes.

Further epidemiologic studies include a study in 2004 looking at female twins. These are unselected twin sets in the United Kingdom. Joint hypermobility was present in 19.5 percent of the monozygotic twins and 22.4 percent of the dizygotic twins.[10] There is concordance for hypermobility in 60 percent of the monozygotic twins and only 36 percent of the dizygotic twins. So heritability for joint hypermobility as a trait was estimated at about 70 percent by these authors.

Rodney Grahame, who is well known to many of you and beloved by many of us in the EDS community, has done several studies looking at joint laxity and benign joint hypermobility syndrome in dancers and musicians. He found in the population of students and professional ballet dancers a very much increased frequency of hypermobility.[11] However, he and his colleagues saw there was also a high percentage with hypermobility in the control subjects: 19 percent of the controls in the upper school population, and 13 percent in the company controls. These are small numbers, so I really don't think we can draw any definitive conclusions from these numbers, but it is extremely interesting.

One other thing I would like to say about the benign joint hypermobility syndrome designation, is that the rheumatologists have for many years talked about benign joint hypermobility syndrome, while geneticists have been talking about hypermobile type of Ehlers-Danlos syndrome. There have been several manuscripts in the literature in the last few years that recognize that what the rheumatologists have been calling benign joint hypermobility syndrome and what the geneticists call hypermobile type of Ehlers-Danlos syndrome are, in fact, one and the same entity.[12,13,14] Definitive proof of this association will depend on the identification of genetic etiologie(s) in well-defined populations of patients.

I believe that joint hypermobility is most probably a continuous variable, similar to height. So we have a continuity of height, and then people who are extra tall on one end with gigantism or Marfan syndrome, and people who are at the far end of the spectrum on the shorter side have one of the hereditary skeletal dysplasias. And I think that the same is true for the connective tissue, that there's a wide variation in the connective tissue flexibility and that it’s the people at the far end of the spectrum that we're looking at in terms of these Mendelian disorders.

The patients with hereditary disorders of connective tissue present with very complex phenotypes, and they're likely to show up in neurosurgical offices presenting with an extensive review of systems. Indeed, most healthcare providers just can't believe that a person could possibly have this number of affirmative responses to the review of systems.

On average, the patients I see with Ehlers-Danlos syndrome have been looking for between 5 and 12 years for a diagnosis, and they have often seen as many as 20 doctors before they've gotten a diagnosis.

They may come in with chronic pain, which is musculoskeletal and/or neuropathic. They have chronic fatigue, sleep disturbances, headaches, TMJ, autonomic dysfunction, mast cell activation syndrome -- which you'll hear about this afternoon -- gastrointestinal dysmotility, lots of GI symptoms and urinary symptoms.[15]

And Heidi Collins, who is the chairman of our medical advisory board for the Ehlers-Danlos National Foundation, likes to say, "If you can't connect the issues, think connective tissues."

So you all can be the vanguard to help identify these patients when they show up in your offices. Thank you very much. Questions?

Discussion following presentation

UNKNOWN 1: So in summary, what percentage of the population would you say have hypermobility syndrome, based upon Professor Rodney Grahame's new data from Great Britain, recognizing that the hypermobility syndrome is essentially the same as Ehlers-Danlos syndrome, hypermobility type?

DR. FRANCOMANO: Well, I've heard Dr. Grahame estimate the hypermobility syndrome may be as frequent as 1 in 100 to 1 in 500; but I haven't seen published data supporting that yet, so I really can't say that that a hard-and-fast fact.

UNKNOWN 2: Clair, when you look at the papers looking at the range of Beighton scores above four in the general population, about 20 percent of high school students will meet these criteria.

I worry that if we equate all flexible people with a disease or syndrome when they don't have all of the features, that we're really doing a lot of disservice labeling people as being impaired or having terrible outcomes.

These days, they almost always, if you mention EDS, they're immediately on the Internet, thinking that their bowels are going to rupture and their arteries will burst; and it's a bit of the issue we have seen over the decades with medical labeling and too much of a diagnostic curse. So I don't know if you have any thoughts on that.

When I looked at the studies from a variety of countries on the prevalence of hypermobility by itself, they're in the range of 15 to 20 percent in high schoolers all over the world.

DR. FRANCOMANO: So this is why I mention that issue about joint hypermobility as a continuous trait, because I do think there is a normal range; and a Beighton of above four, especially in a younger population, may be well within the normal range.

We establish the diagnosis of the syndrome; and the diagnosis of joint hypermobility syndrome requires the presence of joint pain and the addition of other comorbidities. So the hypermobility, in and of itself, would not establish the diagnosis.

UNKNOWN 2: Thank you, Clair.

UNKNOWN 3: What is known about the tissue distribution of the effects of Marfan's or EDS, in other words, ligaments and dura? Is there any information that actually might affect the elasticity or compliance of the brain tissue itself controlling for blood flow?

DR. FRANCOMANO: There is definitely connective tissue in the dura. However, the true extent of the importance of the connective tissue in the brain is unknown.

In terms of Chiari, the tethered cord plays a role as a potential etiology or connection. And also instability at the craniocervical junction if you have lateral instability or cranial settling.

UNKNOWN 3: As a personal observation, people with extreme EDS very often have friable tonsils, as compared to normal tonsils. So I do not have any statistics about it, but it does not surprise me I find them, knowing that the patient is EDS with what appears to be higher rate of co-morbid conditions.

DR. FRANCOMANO: Thank you very much.

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Figure References

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5. Dysautonomia – A co-morbidity or consequence of craniocervical instability and ventral brainstorm compression?

DR. FRASER C. HENDERSON, SR., MD

Dysautonomia is a subject in which neurosurgeons have not dwelt. However, as craniocervical disorders have drawn more attention in recent years, especially in patients with connective tissue disorders, we're appreciating a greater number of problems are manifestations of dysautonomia, which beg the question as to causality or co-aggregation. And so I think Dr. Batzdorf asked me earlier to prepare a talk on the relationship between dysautonomia and brainstem disorders. In particular, does brainstem compression cause dysautonomia? (**Fig 1**)

From the outset, it is important to state that dysautonomia, or dysfunction of the autonomic nervous system, derives from all parts of the nervous system, so that the influence of the craniocervical junction should not be overestimated.

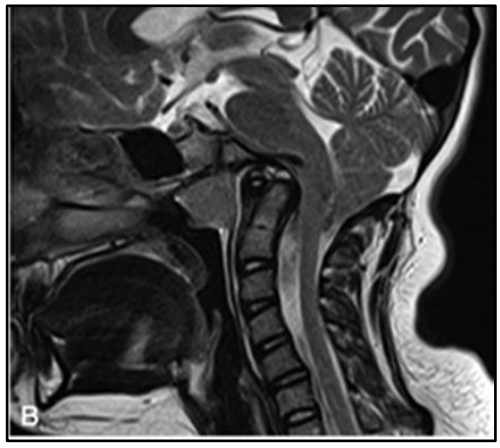

Figure 1 - Sagittal T2 weighted MRI demonstrating severe brainstem deformity as a result of a kyphotic clivo-axial angle.

It's a stratified, ubiquitous problem, and it's very complex. The autonomic nervous system was discovered in 1898 by Langley, who subsequently defined the three components: sympathetic, parasympathetic and enteric. Shortly later adrenaline was discovered, and it was then determined that adrenaline was actually a chemical mediator. Acetylcholine was then discovered, and over the last 50 years many more have been discovered -- peptidergic, glutamate, nitrous oxide and other compounds- that serve as mediators for the autonomic nervous system.

The standard doctrine shows the autonomic nervous system, as descending trunks. The sympathetics, descend through the intermediolateral cell column, exit through the spine from T1 to T12, and affect organs throughout the body. The craniosacral parasympathetic system, which exists in the cranial nerves and the sacral parasympathetic system, which governs the GI system from the splenic flexure down.

The sympathetic nervous intermediolateral cell column transmits through the spine as paired efferents rising and descending in the paravertebral spinal ganglia, the sympathetic trunks; and then as non-paired prevertebral ganglia in the celiac superior and inferior mesenteric ganglia. **(Fig 2)**

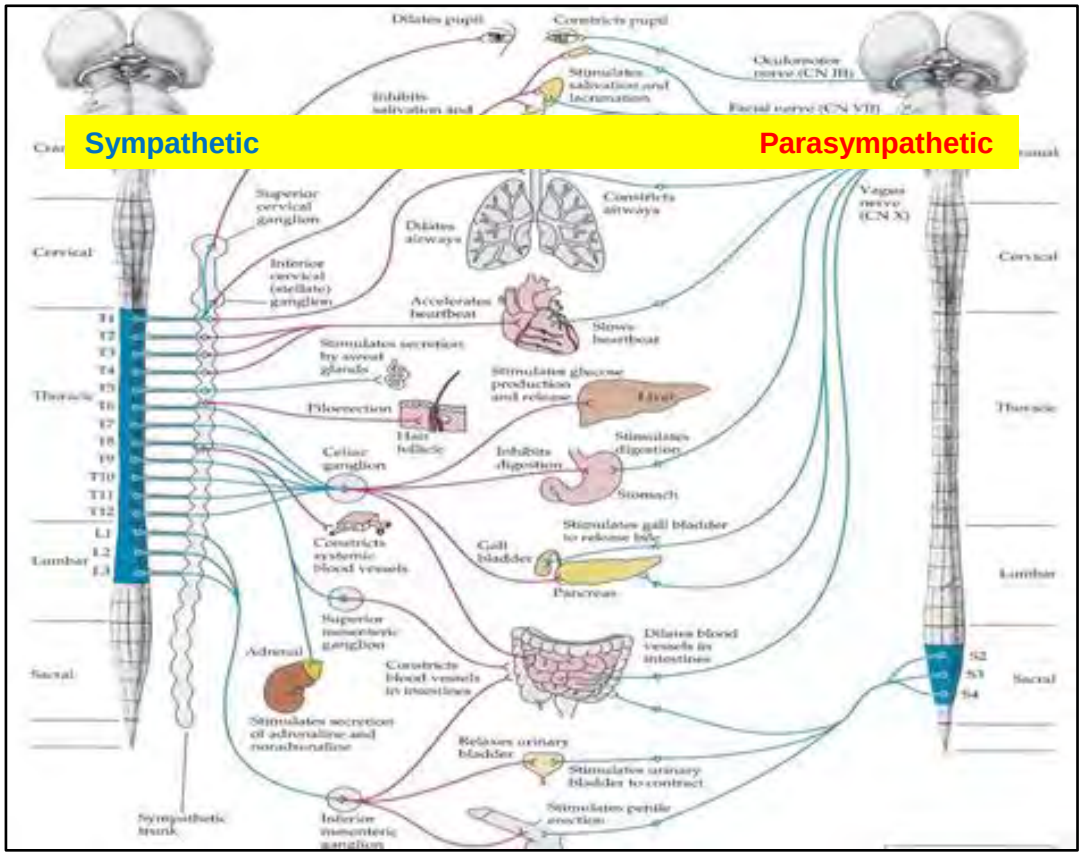

Figure 2 - The contribution of the sympathetic and the parasympathetic nervous system in the function of the organ systems of the body.

It is very important to recognize is that there are sensory fibers that ascend with the sympathetic system, and these sensory fibers are very important in terms of chronic pain syndromes. The craniosacral parasympathetic system: Cranial nerves III, VII, VIIII, and X and the sacral nuclei S2, 3, 4 in the dorsolateral cell column transmit postganglionic neurons that release acetylcholine, activating one of three known receptor subtypes, and very importantly, modulate other neurotransmitters.

So the autonomic control is very diverse, and I'm going to very briefly run through these or some of them. In the GI system cranial nerves V and VIIII stimulate the salivary glands. The vagus nerve stimulates gastric acid and pepsinogen secretion, secretion from the submucous plexus, secretory cells, the pancreatic acinar cells, and cholecystokinin to contract the bladder. Together with the sacral nerves, the vagus nerve modulates transmitters and peptides to control intrinsic muscles of the stomach and bowel. It's remarkable that the understanding of the autonomic nervous system, in terms of its function in the bowel is yet nascent. Generally speaking, however, the vagus nerve innervates down to the splenic flexure and the sacral parasympathetics from the splenic flexure down to the rectum, and may control peristalsis and motility; whereas, the sympathetic nerve maintains continence by contraction of the internal sphincter, and also serves to decrease the blood flow in the bowel.

The sympathetic nerves have other functions in the bowel that are not clearly characterized; so it's innervation of the bowel is more complex, and represents a balance of the sympathetics and parasympathetic nerves. The parasympathetics innervate the intrinsic muscles of the intestines – Auerbach's, Meissner's, and so on – seen on the right. (**Fig 3)**

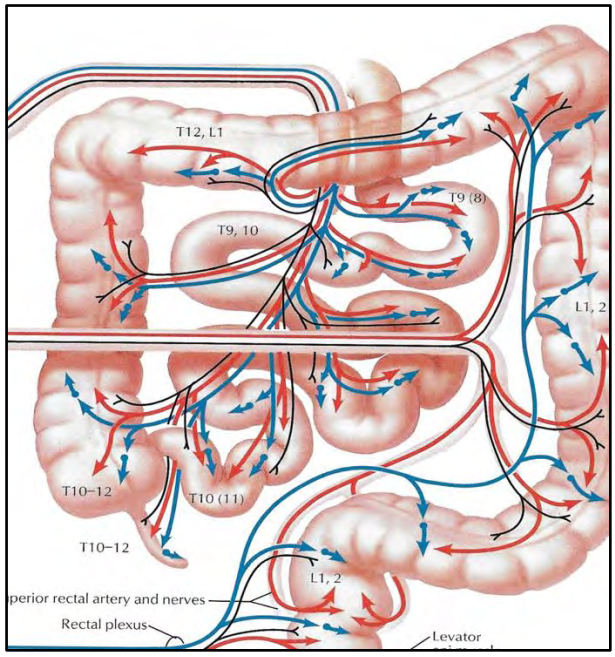

Figure 3 - The dual sympathetic (red) and parasympathetic (blue) innervation of the bowel. The Vagus innervates the bowel down to the splenic flexure, and the sacral plexus innervates from the splenic flexure down.

Blood pressure: The baroreceptor reflexes are all governed by the autonomic nervous system, which utilize the stretch-sensitive mechanoreceptors that maintain tonic activity in a split-second negative feedback loop to maintain blood pressure. These baroreceptors are located in the aortic arch, from which they travel in the vagus nerve; and, second, from the carotid artery they travel in the glossopharyngeal nerve to the Nucleus Solitarius and other parts of the brainstem. Thus an increased blood pressure causes increased firing at the nucleus solitarius, which excites – through glutamatergic neurons- the caudal ventrolateral thalamus, which elicit inhibitory GABAergic neurons (cf gamma-aminobutyric acid, the major inhibitory transmitter in the CNS), causing inhibition of the rostral ventrolateral thalamus. In turn, this inhibition results in decreased sympathetic activity in the preganglionic neurons of the intermedio-lateral tract of the spinal cord, and hence, through decreased sympathetic action, a decreased blood pressure. Increased blood pressure also stimulates the vagal nerve through reflex arcs to slow down cardiac pacemakers.

It is important to recognize that these baroreceptors are mechano-receptors in which that the presence of a viscoelastic coupling may be altered in subjects, diagnosed with hypermobility disorders. The consequences of this viscoelastic coupling are threefold: first, they have a rate sensitivity -- wherein the rate change is more rapid with a high firing rate, the faster the firing the faster the rate change. Second, the effect of adaptation results in a firing rate may be rapid initially, and then tail off. And third, the effect of hysteresis, such that the firing rates are higher with pressure increasing. Knocking out the baroreceptors results in sustained hypertension.

Blood pressure is also controlled through control of the kidneys. This is a negative feedback loop, similar to that just described with the baroreceptors. Decreased blood pressure results in decreased firing in the nucleus solitarius, decreased stimulation of the caudal ventrolateral thalamus, and decreased inhibition of the rostral ventrolateral thalamus. This decreased inhibition results in increased stimulation of the intermedio-lateral cell column fibers, which are in turn mediated through the splanchnic nerve and the aorticorenal ganglia, and finally the endpoint on the beta-1 receptors of the juxtaglomerular

cells. These beta -1 receptors have the effect of increasing renin, hence sodium chloride retention, and increased blood pressure.

Conversely, increased blood pressure has the opposite effect, as well through the nucleus solitarius, decreasing antidiuretic hormone. Thus, increased blood pressure causes increased blood flow to the kidneys and increased glomerular filtration rate.

Autonomic control effect cardiac function: Most cardiac control is exerted through the intrinsic Starling mechanism. Through the Starling mechanism, cardiac output can increase from 5 to 13 liters per minute. However, input from the sympathetics and parasympathetics, can increase cardiac output to 20 liters per minute. Sympathetic input is mediated through the thoracic sympathetic ganglia, especially T6, T7 levels, via the coronary arteries, which affect the sinoatrial and atrioventricular nodes and the myocardium. Norepinephrine affects alpha-1 inotropes- the alpha-1 receptors, exerting an inotropic and chronotropic effects. The beta-1 receptors have an inotropic effect, stimulating the cyclic AMP-dependent phosphorylation of the calcium channels to increase the inotropes.

Parasympathetics of the vagus enter through the neural plexus of the AV groove, affecting the SA and AV nodes, increasing sarcolemmal K, hyperpolarizing the membrane, therefore making it less excitable with the result of a decreasing the heart rate.

The autonomic nervous system also affects the cerebral circulation, notwithstanding the intrinsic mechanisms to be governed by low pH, metabolic needs, and altered blood flow.

There is also an extrinsic mechanism, the sympathetic nerves, which enter via the carotid artery, affecting the forebrain structures, and via the vertebrobasilar arteries, affecting the hindbrain structures. In addition, the nucleus ceruleus, and locus ceruleus can cause brain effects, constricting arteries, but also having a trophic influence on circulation.

The parasympathetics, mediated through the superior salivatory nucleus, cranial nerve VII and the sphenopalatine ganglion, tend to relax the blood vessels. And they work by peptidergic transmitters- acetylcholine, nitrous oxide (NO), and vaso-intestinal peptide (VIP).

Autonomic control of the airways involves the nucleus ambiguous and vagus nerve. The vagus nerve interacts with three receptors in the lungs, including alpha delta fibers that are very sensitive to smoke, histamine, serotonin; and the C fibers that conduct pain. Afferent C fibers (Vagal) can be stimulated by any noxious stimulant causing reflex constriction, mucous gland secretion, vasodilation, increased vascular permeability, leaky vessels, and increased muco-ciliary activity. Adrenergic tone, on the other hand, is regulated by circulating epinephrine, involving the secondary utilization of nitric oxide. **(Fig 4)**

Psychological responses, mediated through the locus ceruleus, can increase epinephrine, and amongst other changes, causing increased cardiac output, inhibition of digestion. It can also trigger mast cell degranulation, and Maitland will be talking more about that. The sympathetic nerves also cause pupillary (mydriatic) responses, hyperhidrosis, Raynaud's-like phenomenon, altered flow to the skin, and the chronic regional pain syndromes.

The causes of dysautonomia are complex and stratified. Stratified, because there is often more than one cause of dysautonomia. Dysautonomia can arise from hereditary conditions, autoimmune injury, fibromyalgia, poisoning, injuries, trauma, hypermobility connective tissue disorders, degenerative conditions, brainstem conditions and mitochondrial disorders. Indeed, one of the six-question test to predict whether a subject has a mitochondrial disorder is "Do you have palpitations?".

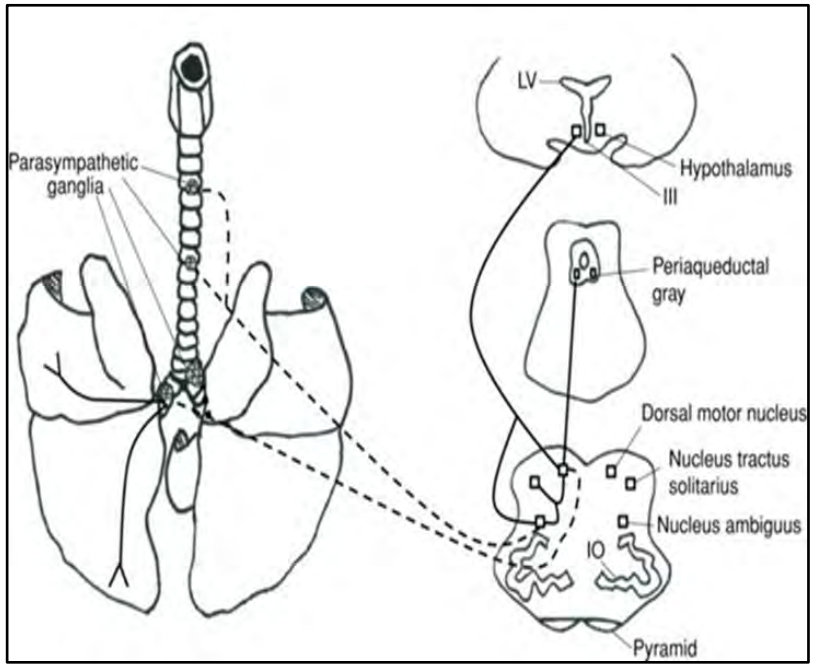

Figure 4 - The Nucleus ambiguus transmits Vagal efferents to M1 receptors in the parasympathetic ganglia of the airway wall. M3 receptors cause bronchoconstriction, and secretion by the mucosal glands through the mediator glutamate. AΔ delta fibers respond to smoke, histamine, serotonin. C fibers transmit painful stimuli.

Dysautonomia occurs commonly in children with developmental coordination disorders. Dysautonomia occurs not uncommonly in post-traumatic stress disorders. And is very common in subjects with ligamentous laxity syndromes, about which Dr. Rowe will be talking later today. **(Fig 5)**

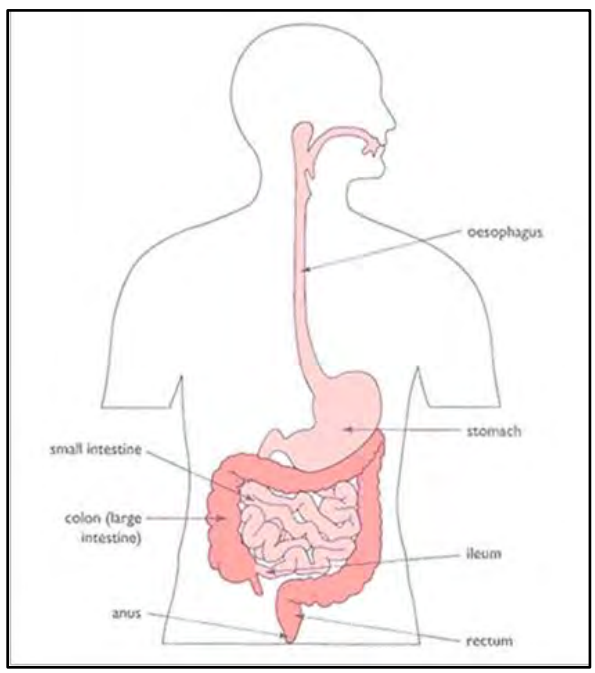

Figure 5 - Dysautonomia in the GI system results in dysphagia, gastric reflux, gastroparesis, malabsorption, bloating, constipation, irritable bowel syndrome, colitis and incontinence.

Dysautonomia may cause Syncope. The Framingham study showed that three percent of the population reported syncopal events, and a slightly higher percentage in women (3.5 percent of the women). This may be due to inappropriate activation of the cardio-inhibitory vasodepressor reflex or other causes of orthostatic hypotension, decreased cardiac output or increased resistance. Syncope is clearly a feature of hindbrain herniation with Syringomyelia and Arnold-Chiari malformation; and there have been many publications to that effect.[1,2,3] Sleep apnea, other breathing

disorders, and altered autonomic function are also clearly established as concomitants to brain stem deformity.[4,5,6,7,8,9,10] We showed, in ten patients with sleep apnea, that the apnea resolved after decompression of the brainstem by transoral odontoidectomy.[11] There is a great deal of literature that attributes the sleep apnea to basilar invagination.

Dr. Rowe, who is probably the world expert on these issues, will be discussing orthostatic intolerance, postural orthostatic tachycardia syndrome, and neutrally - mediated hypotension. Notwithstanding a dearth of evidence, there also appears a significant connection between the autonomic nervous system and mast cell activation.

While dysautonomia has many parts, there appears to be a significant contribution from the brainstem nuclei near to the to the craniocervical junction. For instance, the dorsal motor nucleus of the vagus, the nucleus and tractus solitarius and the nucleus ambiguus. It would seem, theoretically, that deformity of the cervicomedullary junction might, by deformation of the brainstem, alter autonomic activity.

Symptoms of dysautonomia are certainly seen in the Chiari population. The complex Chiari malformations may be burdened with ventral brainstem compression from basilar invagination or odontoid pannus, or platybasia, atlanto-occipital assimilation, atlas assimilation, and craniocervical instability.

The figure shows a patient who suffers a chronic injury to the brainstem from the odontoid pressing into the ventral aspect of the brainstem. This results from backward and forward translation of the skull over the spine. **(Fig 6)**

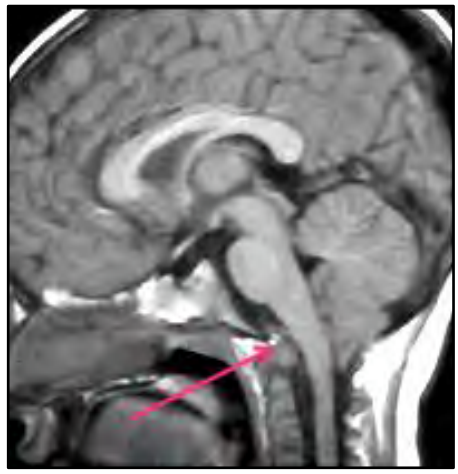

Figure 6 - The odontoid broaches Wackenheim's Line causing ventral brainstem compression. The Chiari malformation I causes some pressure behind the lower brainstem.

A generous sub occipital decompression OA Chiari malformation may relieve the compression posteriorly, but can exacerbate the craniocervical instability in a patient with a hypermobility connective tissue disorder, and thereby increase the degree of ventral brainstem compression.

Atlantoaxial instability may result in dysautonomia, manifesting as syncope. Atlantoaxial instability (AAI) is common in the connective tissue disorders, such as rheumatoid arthritis, systemic lupus; Down syndrome, ankylosing spondylitis, myxedema, and the skeletal dysplasia sand the hypermobility connective tissue disorders such as Ehlers-Danlos syndrome. (**Fig 7)**

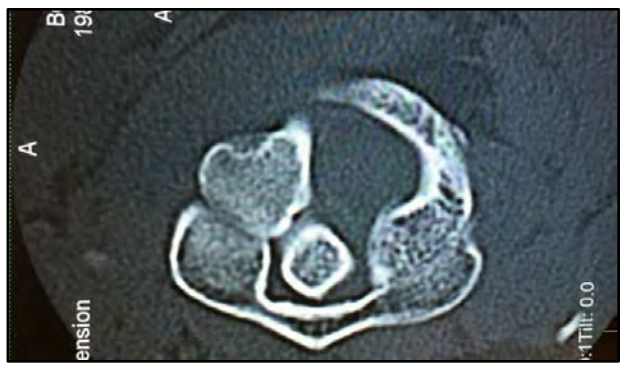

Figure 7 - This axial CT shows more than 44 degrees of rotation of C1 over C2, constituting pathological C1C2 rotary subluxation.

The association of dysautonomia with brainstem and upper spinal cord deformity begs the question as to the mechanism involved. How does deformation

of the neuraxis alter neurological function? The central nervous system is to some extent plastic, molding around any site of deformation.

However, the examination of cadaveric specimens of patients who died of basilar invagination, demonstrates the formation of axon retraction bulbs; and these are the pathological substrate of stretch myelopathy or deformity-induced injury.[12] **(Fig 8)**

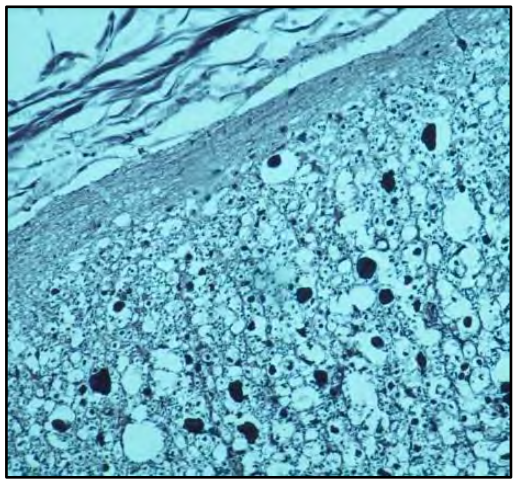

Figure 8 - The histological preparation shows the posterior tracts of the cervical cord of a cadaveric specimen of damaged spinal cord in the setting of basilar invagination: the silver staining shows axon retraction bulbs, which are thought to reflect stretch injury to the nerves.

Povlishok, Maxwell, and Jafari also showed that stretching neurons causes clumping of the neurofilaments- the architectural elements of the nerves- and of the microtubules- the pathways of micronutrients- resulting in the development of these axon retraction bulbs.[13] The same was shown by Saatman[14], who stretched optic nerves, and found the development of axon retraction bulbs that preceded further apoptotic changes. My colleague, Jennian Ford Geddes Montagu in Great Britain showed the presence of axon retraction bulbs in children with shaken baby syndrome.[15] **(Fig 9)**

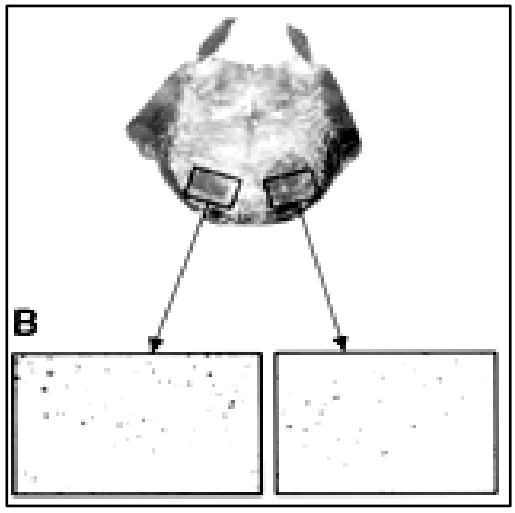

Figure 9 - An axial view through the lower pons with silver staining demonstrates the axon retraction bulbs, thought to result from a stretch deformation event.

Wolf showed that stretching nerves deforms the sodium channels, leading to an influx of sodium, depolarization of the voltage-gated calcium channels, and a pathological increase of calcium into the neurons.[16]

Arundine showed that stretching is an epigenetic stimulus, causing up-regulation of genetic expression, resulting in, for example, increased N-methyl-D-aspartate receptors. These neurons more sensitive, more vulnerable to free radical species, and nitrous oxides.[17] Thus deformative or stretch-induced injury is now becoming generally accepted as an important form of injury in the central nervous system.[18,19] We've certainly accepted the concept of stretch induced neural injury for many decades in the setting of tethered cord syndrome.

Thus stretch injury and deformation causes neural injury, spinal cord injury, and brainstem injury. But what evidence is there that this deformation alters autonomic nervous function? In a multi-disciplinary consensus statement in 2013, it was decided that the cervico-medullary syndrome occurs in association with craniocervical instability and basilar invagination.[20] Cervico-medullary syndrome is composed of many of the symptoms of which we discussed earlier in this presentation.

The importance of the kyphotic clivo-axial angle is being recognized by many authors. And in 2010 we published a work, performed mostly at Georgetown University Hospital, in which we correlated the predicted stresses induced by deformation of the brainstem due to a kyphotic clivo-axial angle. And we predicted these stresses using finite element analysis.[21]

In this study, a dynamic modeling that looked at aggregate strain and deformity and out-of-plane loading was used. It provided these axial images, which were color-coded for various levels of strain. So that orange strain is about 40 Newtons per square centimeter, a very, very high strain.

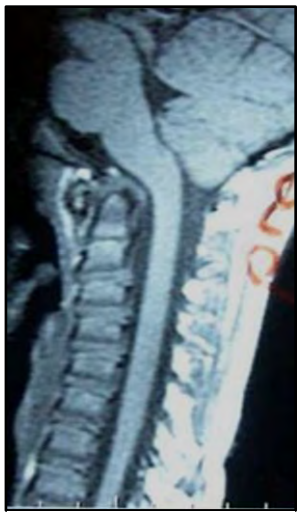

Figure 10a – mid sagittal T1 weighted MRI showing Chiari malformation, kyphotic clivo-axial angle with severe deformity of the brainstem in a young boy

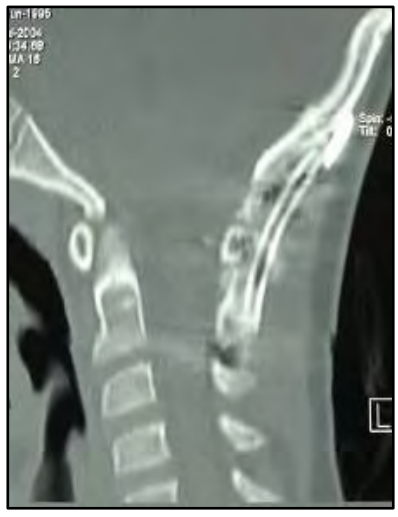

Figure 10b – postoperative, mid sagittal CT view showing correction of the clivo-axial angle and cranio-spinal alignment

So here's an example, a nine-year-old boy who had repeated cardiorespiratory arrests, unable to breathe out, weekly trips to the emergency room, sleep apnea, dysphagia, many neurologic deficits, a clivo-axial angle of 115 degrees. The stresses before surgery were calculated by the finite element analysis and are extremely high in the upper medulla, posteriorly- in excess of 60 newtons per square centimeter. After surgery the stress is decreased to less than ten newtons, shown in deep blue. (**Fig 10a, 10b, 10c, and 10d)**

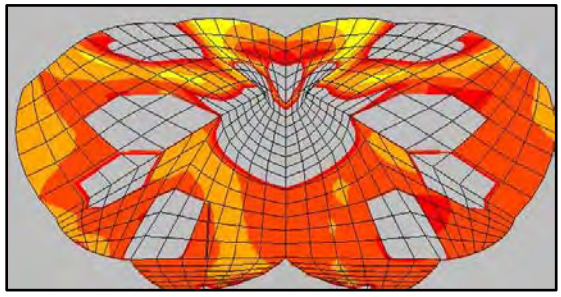

Figure 10c – finite element analysis showing a very high stresses in the lower brainstem pre-operatively.

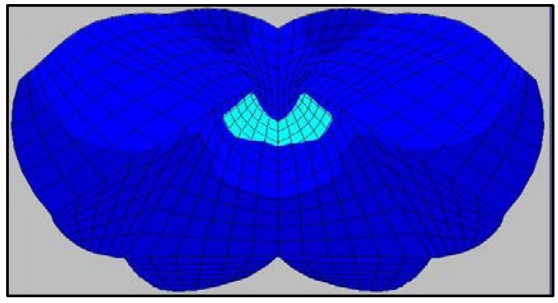

Figure 10d – normal stresses (0-5 Newtons) in the straightened cranio-cervical junction, post-operatively.

The improvement in stress after surgery correlated with the improvement in the clivo-axial angle, the resolution of the brainstem symptoms, improvement of Karnofsky and improvement of pain. This boy was playing sports, obtained his fly, and eventually earned a scholarship to study aerospace engineering. Examination of all ten of these children resulted in correlation of the predicted deformative stress in the brainstem with the clinical metrics. Correlation is not proof of causality. However, this data does suggest that removing the deformative stress from the brainstem improved the clinical performance. Examining the data on a more granular level, could specifically point toward the neural elements of the autonomic nervous system. For in-

stance, the nucleus solitaries, so important in the cardiac and carotid baroreceptor reflexes, exhibited very high strains before surgery and a significant decrease in strain after surgery. So that improvement in deformative stress correlated with the improvement in the many symptoms of brainstem. And these data were all statistically significant, despite the very small number of participants in the study of ten.[22]

In an unpublished study presented to the Army, adults with deformity of the brainstem and upper spinal cord were examined before and softer surgery. The calculated finite element analyses suggested the maximum predicted stress in the brainstem before surgery showed a statistically significant lessened after surgery to reduce and decompress the deformity. Thus mathematical predictions of stress, with finite element analysis, have demonstrated that straightening the brainstem and stabilized the craniocervical junction may decrease the calculated deformative stress of the CNS structures.

In another clinical study of 20 patients with hypermobility connective tissue disorders, we performed a reduction and fusion and stabilization for CCI and basilar invagination. The study is in preparation for publication. Some of the symptoms of dysautonomia were improved. These included fainting, swallowing. (**Fig 11)** Many symptoms were not reliably improved.

But of the patient symptoms pertaining to dysautonomia, there was improvement in only 33 percent of night awakenings, 20 percent of the sleep apnea, 38.5 % urinary frequency, 37% of Raynaud's–like symptoms (hands and feet turning cold in cold weather), 30% of gastro-esophageal reflux disorders (GERD) and 18% of irritable bowel syndrome.

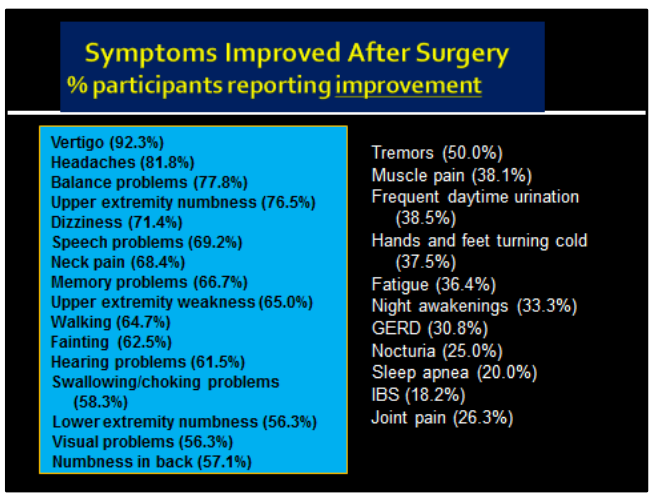

Figure 11 – Symptoms of dysautonomia following surgery

This data, therefore, suggests that all dysautonomia symptoms cannot be attributed to the brainstem. Another recent study suggests that in the population with hypermobility connective tissue the Ehlers-Danlos syndrome population that autonomic impairment is probably multifactorial, involving both the peripheral nerves and the sympathetic nerves.[23] The Ehlers Danlos syndrome population is reasonably representative of the hypermobility connective tissue population. In this population, patient subjects were found to have a higher resting sympathetic activity, but a decreased response to cardiovascular challenges, such as with Valsalva or tilt table or orthostatic response. For instance, the response to the tilt table shows a greater in blood pressure and a smaller, slower correction after the challenge. This suggests that there is impairment of vasoconstriction, and therefore of the sympathetic network.[24,25]

Postural orthostatic hypotension (POTS) appears to occur in 74% of the EDS population, and represents the most disabling manifestation of dysautonomia in EDS. In contrast to the impaired sympathetic nervous system, and its failure to mount an adequate vasoconstriction response to hypotension, there appears to be normal parasympathetic regulation.

The level at which the sympathetic incompetence occurs has not been demonstrated. Peripheral neuropathy has been implicated, and is supported by the prevalence of sensory neuropathic symptoms in these same patients. However, quantitative sudomotor axon reflex testing (QSART), which measures the post-ganglionic cholinergic activity of the skin in terms of sweating, has shown that one third of patients with sympathetic nervous system dysfunction have normal QSART testing. Others have suggested that increased distensability of the vasculature allows for greater vascular pooling during the upright posture. The notion that this collagen laxity in the vasculature underlies the POTS is supported by the finding that skin hyper extensibility is the most important predictor of sympathetic dysfunction.[26]

In conclusion, dysautonomia is common, especially in the hypermobility connective tissue disorders. It is reasonable to posit that dysautonomia may arise centrally in the brainstem, or in the sympathetic tracts of the spinal cord (the intermediolateral cell columns), in the spinal ganglia or in the peripheral nervous system. Anatomically the autonomic nervous system is ubiquitous, and manifestations of its incompetence should reasonably be expected to result from diverse anatomical and physiological conditions. While there is abundant clinical evidence that dysautonomia is associated with basilar invagination and other conditions of deformation of the brainstem, it is almost certainly the result of changes in the spinal cord and peripheral nervous system.

Discussion following presentation

UNKNOWN 1: That list, Fraser, how many of the total patients that you saw – I just needed the denominator.

DR. HENDERSON: I had showed you two studies. The first study was ten; the second was 20.

UNKNOWN 1: That shows us we've got our work to do with the database and stuff. I think it's really, really important. And every patient is an individual. For that denominator every patient denominator is one. But it's very hard to predict which ones are going to get better and when they're going to get better.

DR. HENDERSON: Right.

UNKNOWN 2: Thank you Fraser. You are saying that the fact that dysautonomia does not always improve might reflect its multifactorial origin.

But couldn't it be that it's just damage that's been done, and it's a sign of irreversible changes? And then the question is on top of neurofilament breakdown due to stresses, it could also be that there are some neuro-inflammatory changes.

I don't know what the literature you cited on the retraction bulbs. Had they also looked at microbial changes in the tissue?

DR. HENDERSON: No, they did not discuss the microbial changes, number one. And I think it is very multifactorial and it's very difficult when you pose these questions to the patients. Many of these symptoms reoccur but with less frequency and with less

severity; but they're still present, suggesting that maybe there was some damage, it may take many years for that damage to repair itself. But we have to look beyond the craniocervical junction for all the answers.

UNKNOWN 3: Fraser, this is out of my own ignorance about the finite element analysis. When you showed that effect in the nucleus tractus solitarius intrinsic in the brainstem and showed the high stresses, was that stress due to movement of the head? Or could the stress be just from the pulsations and cardiac pulsations? How is it related to motion?

DR. HENDERSON: We used a finite element program that predicted the stresses created by placing the cervical spine in full flexion. The value represents the relative stress as compared to the spine and craniocervical junction in the neutral position. The calculations did not take into account the smaller stresses, such as from pulsations.

UNKNOWN 4: Fraser, some 20-plus years ago the great physicist Roger Penrose wrote a wonderful book called "The Emperor's New Mind". And he takes all of us biologists to task for ignoring transient changes in membrane physiology related to stress.

And I think, only a comment, that as this proceeds, it's going to be very important to discover what's dynamic, and what's fixed, what's injury, and what is not, because I've always thought Dr. Penrose's criticism was well deserved, and very little has been done since he made it.

UNKONWN 5: Another possible variable complicating the Dysautonomia in general, is that many of these patients are hormonal imbalance. Hormones and the autonomic nervous system have a close regulation. The other thing is that maybe these patients are on medications that somehow do modulate function of the autonomic nervous system in general, and at least may affect other organ systems - for example, bronchospasm or vascular spasm of the heart.

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6. A Conversation on Radiological Convergence of Normal and Pathological Threshold for Spinal Instability

DR. MYLES KOBY, MD

Thank you very much. I've been asked to talk about the normal to abnormal spinal stability. I'm going to focus on the cervical spine. Generally, the purpose of imaging is to confirm a clinical diagnosis, exclude alternative causes and to localize and quantitate the involved problem. We tend to be hopeful that we obtain replicable data. We want something we can assess; we want something that allows us to monitor progression and that provides us with an objective measurement. Historically, instability has been evaluated in trauma, inflammatory diseases and as follow-up for therapy, healing, or fusion failures.

There are a number of measurements for instability. Rotation CT can be used for evaluation of C1-C2 instability. Flexion-extension could be performed with MRI, CT fluoroscopy, and plain films. Lateral tilt can be performed with fluoroscopy and film. And rotation can be evaluated under fluoroscopy.

This is a rotation CT (**Fig 1**) that we are using to look for a difference at C1-C2. We use flexion-extension (**Fig 2**) to assess angulation and translation issues. This individual just couldn't go any further on flexion, she had too much pain; but she had quite a bit of extension.

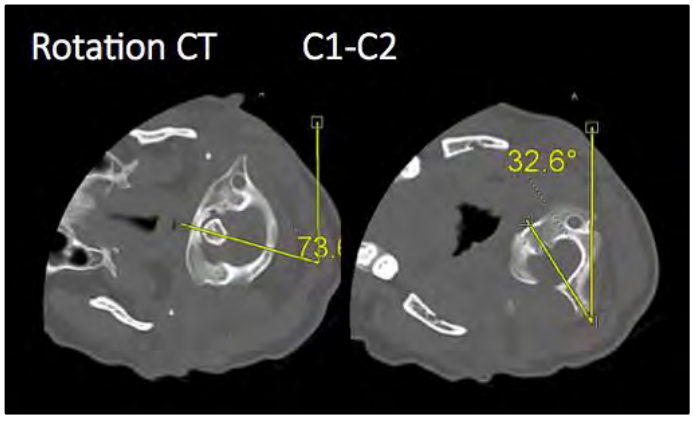

Figure 1

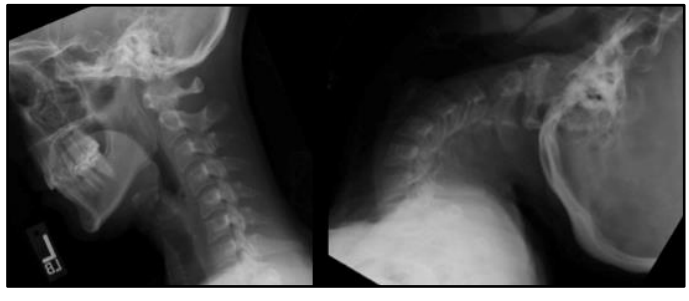

Figure 2

Extension and flexion can be done with open MRI or with CT. It can also show anterolisthesis and retrolisthesis. In addition, these images can show other issues or allow us to look for quantities such as the Grabb-Oakes and Harris measurements. Historically, there have been a number of case series that study the amount of motion that is found within a normal range. The largest series conducted was the Panjabi series that had 500 patients, stratified by age. The investigators concluded that there really wasn't anyone beyond 17 degrees for flexion-extension angulation, outside of standard deviation.

One of the problems, though, is the validity – or what the imaging results actually mean and the significance of the measurements. The big problem, or at least what I think is an issue, is that we look at patients and the severity and duration of their symptoms, but the question remains about what is really taking place.

We're really looking at the maximum motion. We're interested in the largest amount of motion tolerated at that time when patients are really failing and having issues, even when they don't exert the maximum amount of effort. We've chosen 20 degrees at any of the levels of the cervical spine for difference between flexion-extension and 3 mm for translation.

Other features for instability, at least in the cervical spine, include disk height loss, marginal osteophytes, endplate sclerosis, and marrow edema in the cervical spine. We are also concerned with adjacent levels of instability at one level, whether it is superior or inferior. Another problem we encounter is the mechanics involved in patients with longer necks or fused segments who then experience an increased risk of problems at the ends of the fusions.

Inherent issues involved with imaging include cost, radiation exposure, and availability, not only in terms of hardware, but also of interpretation. Replication and reliability of measurements and results become difficult when we see some patients. Issues can include body habitus with the increasing size of individuals, torticollis, scoliosis, and ability to cooperate. There are also issues involving exertion – some patients are limited in what they are able to do; these problems can include fatigue, overall stamina, pain levels at that time, and whether motion is applied in a passive or active phase.

We also have some problems in terms of the interpretation of these images. Problems can include alignment issues, endplate or cortical irregularity, rotation at the time of the study, and overall technique or contrast in evaluating bone.

We must also consider that when we look at images, we are looking at a two-dimensional image of a three-dimensional problem. Typically, the flexion/extension or lateral tilts are nonphysiologic motion. We don't generally do those motions in everyday life. We're using an endplate measurement. Particularly, our patients who are in pain or symptomatic are really not moving around very much and they have already experienced spinal failure.

To sum up, we need to treat the patients, not the images. There are real limitations to imaging due to complex motion. Imaging may help with selection of individuals—maybe it can predict adjacent levels of disease. The big problem that I tend to see is that our patients have failed and they're not really moving in extreme motion, but in a limited motion. I'm not always sure that extreme motion has to be 23 degrees, rather than 21 degrees, to be considered for surgery; and I don't believe that 43 degrees or 42 degrees, rather than 41 degrees, in spine rotation would be a determining factor for surgery, either. Rather, I believe the most important thing to take into consideration is the patient's symptoms. Thank you very much.

Discussion following presentation

DR. PAOLO BOLOGNESE: Down syndrome patients have different ranges of "normal" for their atlanto-dental interval.

DR. MYLES KOBY: Yes.

DR. BOLOGNESE: We know that EDS patients have different ranges for what is considered their own intrinsic abnormalities or their own range. The other complicating factor is that many EDS patients are not the same. Some of them are more hypermobile, but they are not uniformly hypermobile. Some are more hypermobile in their large joints; others, in the small joints; others, in combination; others have some joints busted as a result of trauma, and others do not.

Without going into the complicating trauma, what do you think is the average increase in (average) normality in an EDS patient? While it probably does not exist, do you think there is some sort of ideal average? Ten percent? 25 percent? Shoot a number.

DR. KOBY: I would absolutely have to guess because nobody has put together a series of patients with EDS who do not have critical symptoms and issues. The patients that I am seeing, I think, are about the worst five percent— people who are failing and in a really bad way.

It might be interesting to do a series imaging siblings or individuals who have EDS but are not failing in their spine. No one has done a series on those individuals.

DR. BOLOGNESE: My current problem is really the understanding of the C1-C2 rotation and diagnosis of rotational instability. I have seen some numbers, but still, I really do not have a sense of what is "normal" for the EDS population.

Obviously, we are treating the patient, not the imaging. So what we sometimes find are rotational "abnormalities", even if the patient is doing perfectly fine. I would just have a better indication of a treatment plan, if I had more of a sense of an acceptable margin of normality for EDS patients, as well as what values lie more in a grey area, before the patient becomes hopelessly pathologic.

This is a big problem because none of the published series discuss that their patients have EDS or any hypermobility issues, they merely identify them as normal controls.

Another problem concerns the patient who has EDS, is very symptomatic, and has only slightly elevated motion because the muscles are in spasm, or they may just have too much pain when they're turning. Or wear and tear on the joint.

DR. KOBY: Yes. So there is a lot of weakness in these numbers. This is something that makes us really hope that we will one day see something more conclusive in order to determine whether the surgery is necessary. The data is just not out there and I'm not always sure what that is going to mean for patients.

DR. HENDERSON: If I can make a comment: it might be fallacious to suggest that there is a different set of normals for the connective tissue disorder population. It is quite possible that this particular population should be regarded using the same set of normals that we use for the normal population because, after all, the nervous system inside is the same and is susceptible to the same stresses. I'm not sure that we really have to look at the EDS population and define a new set of normals. They are abnormal; that is the problem.

DR. BOLOGNESE: So the end product is the effect on the distortion of the brainstem. Your point is not really what is happening to the bones, rather, the endpoint is what happens to the nervous system, in terms of distortion?

DR. HENDERSON: Exactly.

DR. CLAIR FRANCOMANO: I wonder if you can comment on the best way for us to use imaging when we are wondering about venous insufficiency. I know that there is a protocol at Hopkins where they perform CT angiography looking at the venous phase. At my institution, we have the option for MR venography. What do you think is the best test?

DR. KOBY: I favor MR venography because it does not take long and it actually is concerned with flow or some element of fluid dynamics; whereas, the CT venography, if it's not caught earlier— often earlier than I am able to do it—there is frequently a balance point where, whether it's high flow or low flow, the venous system opacifies, unless there are frank filling defects.

7. What We Have Learned: Park-Reeves Syringomyelia Research Consortium

DR. DAVID LIMBRICK, MD, PHD

Thanks for your attention. I actually do not have a formal presentation. I was going to give an informal presentation yesterday to the CDE group, the Common Data Elements (CDE) group, but I had some travel challenges so missed it. I appreciate everybody giving me the opportunity to make it up now.

I am the principal investigator for a registry called the Park-Reeves Syringomyelia Research Consortium. I am going to share some of my experiences with this registry. Some of these experiences will be applicable to the larger CDE and registry efforts proposed by CSF, and some will not. I do have some disclosures, but none of them are relevant to today's discussion.

The Park-Reeves Syringomyelia Research Consortium consists of a large group of investigators— all work being pediatric in nature. The registry is based out of Washington University in St. Louis, Missouri which is where my group is located. St. Louis Children's Hospital is the clinical coordinating center. The data coordinating center is hosted at the University of Iowa by Jim Torner, that center's PI. There is an advisory board and then the team itself. As of today, the team consists of thirty-five major children's hospitals with over fifty investigators.

I just want to sort of introduce this because as we talk about doing a registry on a larger scale, I think we need to think about how all the parts fit together and who the different stakeholders might be. This is the list of all the different children's hospitals that are a part of Park-Reeves. **(Fig 1)** Right now there are 35. I'll get to this at the end, but I recently put together a proposal for a randomized control trial, which will expand this to 50 hospitals. Again, we will talk about that in a little while, but it is really an enormous undertaking.

PRSRC Collaborating Centers		
All Children's Hospital	James Witcomb Riley Hospital for Children	Stanford University
Boston Children's Hospital	LeBonheur Children's Hospital	St. Christopher Children's Hospital
Children's Healthcare of Atlanta	Los Angeles Children's Hospital	St. Louis Children's Hospital
Children's Hospital of Colorado	Lurie Children's Hospital of Chicago	Seattle Children's Hospital
Children's Hospital of Wisconsin	Mayo Eugenio Litta Children's Hospital	Texas Children's Hospital
Children's Hospital of Philadelphia	Memorial Hermann Children's Hospital	University of California - San Francisco
Children's Hospital of Pheonix	Miami Children's Hospital	University of Iowa
Children's National Medical Center	Nationwide Children's Hospital	University of Michigan
Children's of Alabama	Oregon Health & Science University	University of Minnesota Amplatz Children's Hospital
Cincinnati Children's Hospital	Pennsylvania State University Hospital	University of Wisconsin Children's Hospital
Columbia University New York Presbyterian	Pittsburgh Children's Hospital	Vanderbilt Children's Hospital
Duke University Children's Hospital	Primary Children's Medical Center	Wake Forest University

Figure 1

You should know that the way that we have structured this is with

two different kinds of agreements. Of course, there is a central IRB, which is disseminated; and then each site has to have their own IRB, which is a variant on that central template. There are now central IRB services, like IRBshare, which I would strongly recommend thinking about for any sort of multi-institutional investigation.

This is the enrollment through last year. **(Fig 2)** We had initially envisioned Park-Reeves to be a three-year data accrual, and our goal was to hit one thousand. Happily, and for the first time on any sort of clinical study I've been involved, we were able to hit the number of one thousand. In fact, before we knew it, we were above one thousand, which meant we had to go back and get IRB approval to even continue the study.

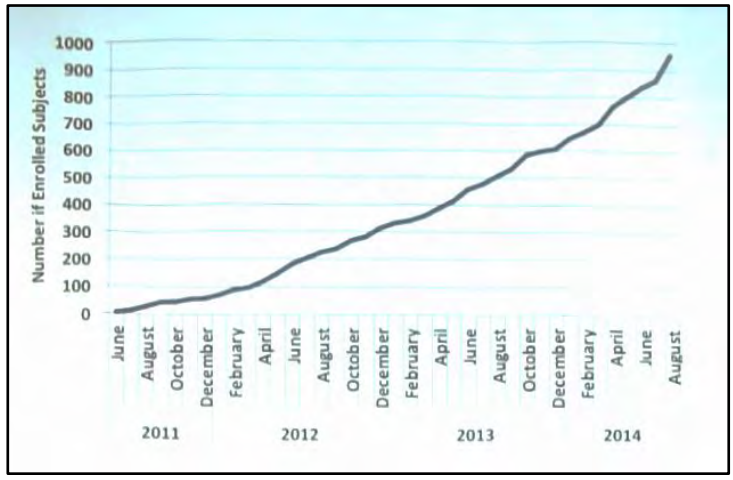

Figure 2

We initially thought we were going to get about a 30 percent prospective— meaning, the consent for the study would be signed prior to surgery; and about 70 percent retrospective. That might be another thing to think about going forward: should we only be thinking about this larger, international database as assessing prospective patients, or are we going to allow some retrospective data to be input?

It turns out that the vast majority of our data so far has been retrospective. Our goal was 70 percent, but it is actually closer to about 82 percent. We initially asked for, at least, two years, but then we changed it to five years of follow-up for retrospective patients.

It also turns out that most of our investigators are neurosurgeons and most do not typically follow their patients out beyond a year. I know that in general most people, I think, advise following for five years; but that just was not realistically happening at many of our centers and we had to rein in our expectations a little bit there.

Over three years we were able to hit the enrollment target of one thousand. Now, we are assessing prospective, only. That works pretty well for us.

The registry itself is an enormous document and with thousands and thousands of different data fields. I'll circle back on that in just a bit because I'm not sure if a broad international database needs thousands of data fields; in fact, Dr. Cormac Maher, who many of you know, is a strong advocate for making the data dictionary an achievable one; and I think there's something to be said for that.

So we structured the registry almost like a history and physical. We started with demographics. From there, we included diagnosis, childhood history, developmental history and so on.

Because this is an entirely pediatric study, we felt like it would be interesting and potentially important to get antenatal data as well. It turns out, however, that exposures such as a maternal history of smoking or alcohol use, taking folate during pregnancy,

and a handful of others would not be included in the childhood history but rather the mother's history, depending on the institution. So, due to some idiosyncrasies like that, we were unable to collect that data from all institutions if that was considered mom's history. This is just an example of some of the very interesting things that we have learned along the way.

In regards to family history, we, of course, are tracking twins, siblings, primary relatives with Chiari and syringomyelia.

And then, of course, we get to medications. We had initially thought medication was going to be a straightforward category; but, over time, medications are up and down, patients go off the medications. It turns out that medications are among the most complicated data fields to track in real-time using a registry.

Other data fields include physical examination, clinical course and treatment. The latter is sort of where the money is at— that is where we looked at every possible type of clinical management from observation to orthosis, for example; cervical collar to decompression.

We tracked anyone who had surgery for a syrinx. That is also where some complications rest. The reason we tracked it in that way had to do with future treatment. If they had any additional procedures, they would all be a part of this clinical course and treatment.

We found that tracking follow-up is very, very hard to do with a diverse group of neurosurgeons or clinicians. For example, certain people would swear by seeing somebody to check their wound post-operatively at two weeks; others at four weeks. Some would see patients once and then see them at one year, whereas, others would see patients more frequently. It was just extremely challenging to make follow-up recommendations to a group of clinicians like this, who had real-time demands.

So what we ended up doing was to group our complications in two groups. Complications could be grouped as being under six months, which would include wound infection, et cetera and greater than six months, which would be more likely to be cervical instability and things like that. We tracked all complications along the way, however. Radiology is a very interesting topic, but I would like to come back to this in a little while because I have a recommendation for the proposed registry.

To quickly reiterate, follow-ups. Again, the way we tracked follow-up was a new entry linked to the initial person's code going forward. So some people may have 20 or 30 follow-ups, some people have only one or two. The variation is based on physician practice.

Our registry is only using clinically indicated scans; we do not fund any scans. We also just use standard of care. For example, if we thought it would be of interest to get a lumbar MRI to rule out a tethered cord, we would not be able to do that since we do not have the funding to facilitate that scan. Park-Reeves was founded entirely through a philanthropic donation from a single family, so we did not have the budget to enable any sort of additional testing. In fact, our investigators were very strongly against additional demands from us for perhaps a cervicothoracic MRI if that patient already had a brain MRI. They did not want to change their practice for observational data, alone.

So for someone to access the registry, he or she will have to log in. You will log on; and depending on who is logging on, you will have certain permissions. Most centers have a research coordinator as well as an investigator who can log on. Users are able

to look at data in a different way, depending on their role. The PI, one central nurse coordinator for the whole database and our radiology experts can view everything.

The idea, though, is to have a platform that allows an investigator at Johns Hopkins or any of the other hospitals to look at his or her own data, and actually analyze that data without being granted access to data from elsewhere, unless you have a proposal that has been approved to survey the entire database. Our IRBs strongly encourage that. So how it works: when you are looking at your data, you will see a list of patients. When you click on a patient, that name is highlighted and you can flip between tabs, depending on whether you are interested in demographics, childhood history and so on.

To come back to antenatal history in practice for a moment, I just wanted to highlight that point about maternal history versus antenatal history again. When you really think about the clinic offices that are collecting data like this, do you really think that everyone is going to collect whether or not there was fetal alcohol exposure? It is fields like this that going forward, if I were to tweak this a little bit, I would not collect this data. I would instead choose to have certain fields that are more important, but other fields where maybe only ten percent of the full data is going to be filled out, I would choose to drop.

We included a full neurological examination, trying to capture everything— strength, sensation. And that sounds great; right? We all want a full detailed neurological exam, musculoskeletal exam. We want all those things.

But, it turns out— and those of you who are neurosurgeons in the crowd will understand— how often are you checking joint position sense on the follow-up at one year following surgery? It is not so common. So in setting up a registry, one really needs to think realistically about the fields before they are added to the registry. There are certain fields that are completed religiously, and there are certain ones that are more liberally interpreted— by that, I mean not really completed. For example, a lot of follow-ups will consist of merely, "Doing well, strength is five out of five throughout, sensation intact to light touch, patient doing well, see you in a year." That sort of data completion examination makes it very challenging to have these data work for us down the road. So for anybody who is going to contribute to an international registry, I think you have to think about really encouraging those individuals who are seeing that registry up to include certain exam components that can allow them to examine and see patients quickly but are also able to give you the data that you need.

I have had a few pitfalls along the way. Number one: in a naive attempt on my part to try to capture everything and learn as much as we possibly could about every patient in our registry, we found that maybe that is not the best thing to do. Instead, what you want to do is capture specific kinds of data. First, they have to be data that you can actually capture— and that is important; second, they should be data that you think is most relevant. If data entry is overwhelming, people will not do it. We have heard that research coordinators doing multiple studies find our study to be more difficult and more exhausting than others.

I would discourage against the use of open text boxes, like genetic condition, osteogenesis imperfecta, Stickler syndrome, and "Other."

"Other" is difficult because the minute you have "Other," that means that somebody with one thousand patients may get to that "Other" category and then have to quantify it for multiple patients. Genetic conditions are probably a bad example because

genetics is actually very important but you can imagine other scenarios where the "Other" box will make it hard to actually extract useful data. It also allows people to be a little bit lazy; right?

In the hydrocephalus registry that I participate in, there is an “Other” box. I have noticed that if an investigator does not really have the time to go back and figure out whether or not the aqueduct really closed, or whether something was communicating hydrocephalus, it is infinitely easier to just to choose "Other." So, ideally, you really do not want to do that in a registry.

Time. Finding time to fill this out is a big issue. It is one thing if you have a research coordinator that can help you, but the majority of people do not have that luxury. So especially as you think about an international database, I think you need to pare down the database so that it is something that can be completed by a clinician or someone who is a busy person and may be forced to sit down and fill it out on his or her own.

Missing data has to be imputed— a very challenging and detailed process as well; so again, that is just another argument against text boxes.

The way that our registry is essentially set up now, we pay $1,000 per patient, which, I think, is a very large sum. I think that has to do with the way we have done it and how detailed the data fields are. We feel like we can ask people to spend time on it because we are reimbursing them for that activity.

If the idea for the international registry is to have people volunteer their time, I think we really have to take that into consideration. We definitely need to have people that have expertise in the field complete this. I think many people would initially try to have medical students or other things come in and try to fill these out, but that is not a good way to ensure that you have high quality data; so we eliminate those kinds of options.

Then, of course, it takes some money to support the registry, not just the initial generation of the database but also database maintenance. If there is to be some sort of webmaster it will take some money. I think that we may have to think about that: budgeting, not just for the first year or two while it is being created but also for maintenance issues and so forth.

This is one thing I wanted to bring up, and I know we have talked about this a little bit on the CDE phone calls: the CNDA or the Central Neuroimaging Data Archive. Park-Reeves uses this. It was developed at Wash U, but it is an NIH thing run on an XNAT platform, which is an open-source platform now. Hydrocephalus Association also uses it for the Hydrocephalus Clinical Research Network (HCRN) and the Adult HCRN. It is basically a free program developed in conjunction with the NIH that does an excellent job of allowing you to archive all the films from any individual patient. So we have enrolled a thousand patients in Park-Reeves, but we have over 5,000 sets of images in the CNDA.

But this point brings up another issue; right? Storage capacity. You need to have a server or a virtual server in a server farm in order to enable data collection for that. This is just something to think about. For example, having multiple MRI scans in follow-up is critical to look at the syrinx size over time; but all of that requires storage capacity. The advantage of using a system like the CNDA is it automatically de-identifies the images as they are uploaded and then gives you a toolbox of instruments in order to make measurements and things.

The CNDA is linked to the Park-Reeves website. We actually have a central radiologist who is the chief of neuroradiology at St. Louis Children's, who works with a fellow. Everything is read by the fellow and then over-read by the chief of neuroradiology which is great for data assurance, but at one point a couple of years ago he said, "Look at all the different measurements that you are asking us to make."

And this is just a partial list; right? (**Fig 3**) So foramen magnum, the diameter, McRae's, McGregor's, Chamberlain's— and so forth. They eventually said, "You know what, this is taking way too much time, we just cannot do this."

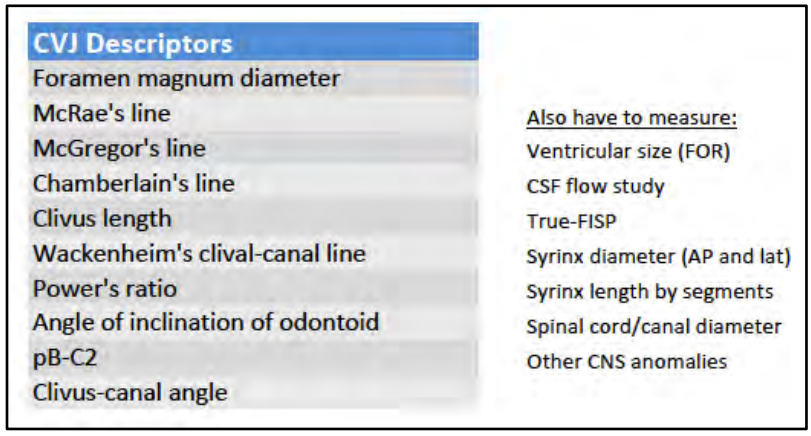

Figure 3

So, as a group, we ended up deciding to pare it down to six fields. These are now the ones that we record. All the films are still on the servers, but the following are the fields that we record for every patient that comes through the registry. These include: tonsillar descent or ectopia, tonsillar position; pB-C2; clivus canal angle; FOR, a ventricular size measurement; CSF flow and cine true FISP, which is a dynamic tonsillar pump pulsatility sequence; and, of course, syrinx diameter and length.

We keep the films, obviously, in perpetuity. And what we would encourage, if people are interested in looking in more detail at some of the imaging, they can go back on their own time or, if they have a grant, they can fund the radiologist to go back and make some of those more detailed measurements. The six I just listed are simply the cohort of measurements that we agreed as a team to measure.

Another thing that was important for us was essentially to come up with a set of bylaws, which I would really, seriously recommend. Even if it the registry is an international, multi-institution, huge registry, I think you need to think about how somebody might be able to enter a proposal, how they will to study the data, and then how to the data can be extracted out and analyzed.

Even in our group, which is just 35 centers right now, we have people who want to study the same things. Everybody wants to study pB-C2 and clival canal angle and outcomes. Everybody wants to do it. So we created some bylaws that allowed us to act as a sort of coordinating center to oversee the studies that are being done and make sure that there are not multiple people doing the same thing. We do not ever limit what can be done, but we do try to make sure that people who are interested in studying the same thing are coordinating efforts or that there is no overlap. I think that this is really important because, otherwise, there is a lot of competition, even among investigators.

I think the reasons to have this policy in place are to produce the best high-quality results and presentations, to encourage multidisciplinary projects and to have the ability to rapidly disseminate findings. We try to never have a "waiting period", in terms of making the data available for our investigators; but we do have this one week where

we permit ourselves to make sure everything is in line with what is being done in other aspects of the registry and with other investigators.

More recently, as I said, we have kind of reached a landmark, which is the end of the retrospective enrollment, and focusing on prospective, only.

This sort of harkens back to the process by which you get something like this funded. Nobody, as far as I know in my experience, really funds an ongoing registry; right? That is really hard to get funded in any disease, for the most part. I think you can get the initial set-up funded, but to have it be funded in perpetuity from a group like the NIH is extremely difficult.

What we really have been encouraging people to do is to submit grants that leverage the data already in here. One example includes a proposal to study posterior fossa decompression with duraplasty with this so-called extradural or bone-only decompression. I am not really going to show any data today but rather just let you know what it is that we are doing.

We propose a major, multi-center randomized control trial for this question of posterior fossa decompression with duraplasty (PFDD) and without (PFD). In pediatric neurosurgery, this is a very important question. This proposal will, of course, make use of the registry, which will help to fund a portion of the registry, the research coordinators and the database management that are all important to go along with the study.

We threw together some data in a couple of days looking at the different complications associated with PFDD and PFD and applied to PCORI to fund the trial. We should be finding out in the next week or so about this. But I wanted to say a few words, as I know that we are thinking as a group about submitted a proposal to PCORI to fund a meeting of experts to essentially develop the CDEs and sort of brainstorm into how we might transition that into a registry.

PCORI, as I think the people who are really actively involved in this proposal know, is very unique. It really is quite different from the NIH and I did not really have a sense of that initially going in to this. PCORI is incredibly interested in having patients, patient-partners, non-physician clinicians, and organizations like CSF and others becoming key stakeholders of these grants. By the time you submit your letter of intent, you had better have sort of gone through the stages of asking all these different people for their input, in terms of making a proposal. It is critically important. I have a friend who is on the study section of PCORI that says that the patient engagement is as important as the science.

In fact, the review committee consists of— I believe—either two or three people who are essentially patient-partners and two or three who are scientific reviewers. So the review is giving equal weight to these engagement sections as it is the science.

The other thing about this proposal process— at least for our group— was that it was fast-paced. After I submitted our letter of intent, I thought, "Whew, I can relax a little bit." But PCORI got back, and said, "Thank you very much, your letter of intent has been accepted. You have five weeks to write this grant."

So my one bit of advice is that we should be writing this grant right now, even before the letter of intent goes in, because it is challenging to get something like that into a good form before submission.

The PCORI budget is not like standard NIH budget with subcontracts. Each PCORI has a contract with each institution. So that is a little bit unique. I am not sure

that is relevant for this meeting per se, but it is an interesting difference between the NIH and PCORI and I thought I would mention it.

One of the last couple of things I wanted to mention about, at least, our experience is that there was really not a whole lot of contact with the program officer. I spoke to them once or twice; but it was almost all virtual via e-mail. Even the correspondence, if you have a question, most of it is done via e-mail. That, again, may be a little less personal than what I have seen in the past. So that was new to me.

The last thing I will say, which I have already mentioned today, has to do with IRB. Having a central IRB service is really important to PCORI. They hold your feet to the fire, in terms of making your time lines. IRB approval, across 50 institutions in our case, always takes longer than an investigator suggests, so they really want you to use a central IRB to expedite the process. And, again, IRBshare is the one that we are using. PCORI made it very clear that a smooth IRB process was important so as not to be waiting, while their funds are being disbursed on administrative details.

I think that was all I had to say. Again, I appreciate your letting me kind of slip in here between all the lectures today and for your attention.

Discussion following presentation

DR. ROGER KULA: I just have a question about whether any aspect of your registry has patient input, self-report forms or anything like that? Is it all investigator input?

DR. DAVID LIMBRICK: That is absolutely an excellent point. I think when we first started this, which was back in 2010 when we were conceiving of Park-Reeves, we mainly thought of it as physicians' input, gestalt opinion and objective neurological exams. Since then, we now have a number of different quality-of-life instruments that we use.

We use the CHIP, which is the Chiari Health Index for Pediatrics; we use the Huey 3; and then the SF-36.

DR. DONLIN LONG: To follow up on that, I first would like to make a comment to the rest of the audience: if you are not experienced with this kind of thing, you have just had a remarkable introduction to this kind of study.

That was more well described information than I have ever heard before from anyone talking on this. And I would say, you and the others involved in that are really to be congratulated.

You should also be congratulated for the thousand dollars per patient. The average cost right now in a drug device study is thirty to fifty thousand dollars per patient. I do not think we will ever reach that level in what we are doing. The thousand dollars is what we did in the national back pain study 25 years ago. Doing a registry for a thousand dollars today is truly remarkable. We had 5,000 patients followed for up to ten years.

But the final point was you have to always remember that you have to prove that your data collection is accurate and you have to continue to prove it on a regular basis; it has to be audited constantly; and you have to be able to prove that all of your outcome majors have statistical validity.

And in the national back pain study we developed the lumbar spine outcomes questionnaire, the cervical spine outcomes questionnaire; both are statistically valid for outcomes, and they can be administered by telephone in two to three minutes by anyone. These surveys do not have to be administered by a trained professional. I think that kind of thing needs to be added to what was a really insightful presentation.

DR. LIMBRICK: Thanks so much for saying that. I could not agree more. The thousand dollars is something that when you think about it, we were also acquiring retrospective patients. And certain institutions would go, if they were motivated, and they would find a hundred patients, and they would put them in very rapidly. And that would be enough to cover a research coordinator's salary for a couple of years.

Others sort of took this sort of prospective thousand dollars at a time, and that was not very much money in that situation, you are right.

On the quality-of-life instrument, we are fortunate. My co-PI on this is a quality-of-life-in-Chiari person, Dr. Chevis Shannon, and she developed something a little bit longer than that. The CHIP is fifty questions, and the parents usually fill it out. But I think it is a great idea to make it even just a few seconds, couple of minutes.

Thank you.

8. Intracranial Pressure and Water Exchange in the Brain: What Scientists and Engineers Think They Know

DR. ANDREAS LINNINGER, PhD

I would like to thank Dorothy and the organizers for keeping this dialogue going between both clinicians and people like me who are not trained in medicine, but who are interested in putting scientific education and background to use in understanding the brain and who are also interested in helping patients. For many years I've been working with the CSF group, and for ten years, I have focused my engineering interest on studying the brain. I think it's very important that we have these conversations between the disciplines to discuss the insights we all have about the brain, so that better decisions can be made for patients. But today, I will do something that is unusual for a scholar to do.

Usually, scholars will come forth with some kind of competence and teach the things that are already known. Today, I want to talk about things that I don't necessarily understand. Maybe my colleagues know and understand, but my suspicion is that we all have a problem understanding intracranial pressure. I would like to share with you my concerns about intracranial pressure and how to get a handle on intracranial pressure, since it is so important for all of you, clinically. My talk today will be a sort of confession about how little we understand about the physics of the brain.

Here's my sketch of your world (**Fig 1**), the way I understand it. My interest is mainly in hydrocephalus, which I think has some parallels to syrinx formation. I am not an expert in Chiari, so please forgive me if my focus is more on hydrocephalus than on Chiari malformation.

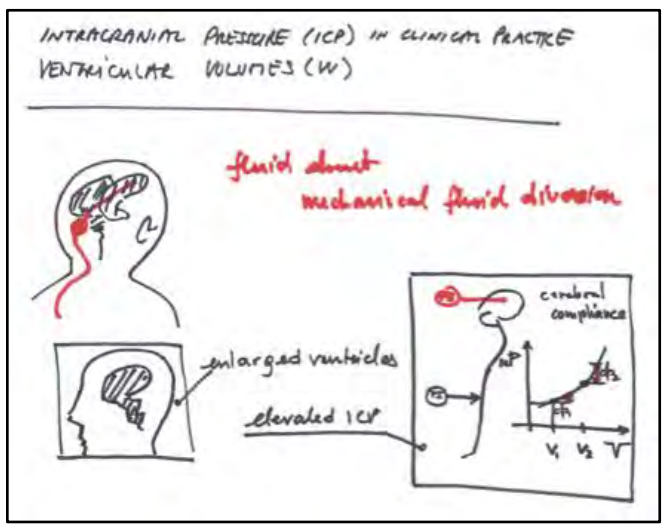

Figure 1

From what I understand, roughly speaking, the management of hydrocephalus includes the management of intracranial pressure and volumes within the ventricles. Anomalies occur in large ventricles that you can see with imaging. You may have pressure measurement scales available. But you know that when intracranial pressure is elevated, it's dangerous; you can find out whether the pressure is elevated with a tap.

We also speak often of cervical compliance. We know that, given the compliance curve, a small volume infusion may result in a large intracranial pressure rise; but when we have a lot of compliance, we may have a very small volume/pressure rise for the same volume that we check. So you're dealing with volumes, pressures, and with shunts that mechanically divert fluid if it's flowing improperly.

In the sciences, we also have to be concerned with pressures. This is a slide (**Fig 2**) from an undergraduate course that looks at flow through tubes. What this shows is that you can balance physical quantities in a deterministic landmark. So, for instance, we can say that if there is no leak in the tube, then the mass that goes in and out, even though it goes through a constriction, needs to be conserved. That's known as the continuity equation of mass conservation.

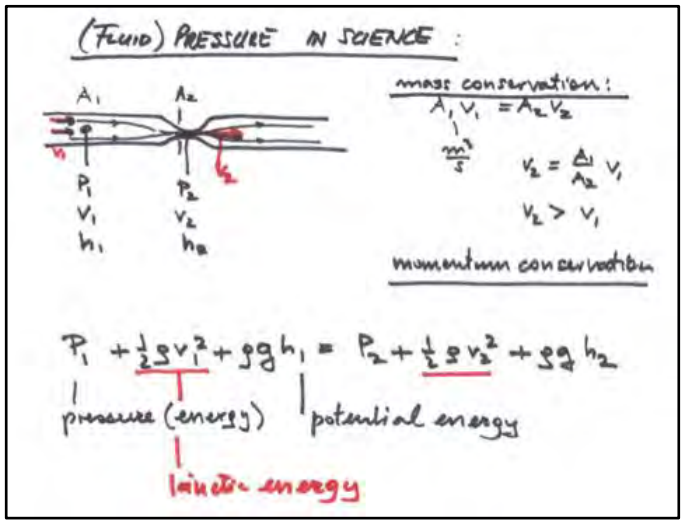

Figure 2

A little bit more abstract is momentum conservation, which involves maintaining the inner energy of a system. In the particular case of the Bernoulli equation, you have something that you all will be very familiar with: the potential energy and its relation to the elevation of the head. When you lie down, the potential energy changes. So this is the world of physics and the real world.

The kinetic energy is the speech, which will change with constriction. Then there is the pressure energy, which is the potential that you need in order to drive through it. This pressure is known to us as absolute pressure, hydrostatic pressure or dynamic pressure, because when we have a constriction, this pressure can change. Is this pressure related to what you all deal with in the clinical setting?

More in detail, computational fluid mechanics is a tool that has been very successful in making an entry into cardiology and cerebrospinal fluid (CSF) dynamics. We also have mass conservation and then a more complex version of momentum balances—the same that I had shown you before. But what I want to point out is that in these balances, we also have a relationship called the 'equation of state', which is the dependency of pressure and density on temperature.

Most of the time, we talk about fluids that are not compressible, so we don't account for the equation of state, we just assert that the density, approximately, doesn't change. Then, we have only mass conservation and momentum conservation. The interesting consequence of that is that when making the Navier-Stokes equation, the pressure occurs only as a difference; there is only an energy change, which has to account for friction. So anyone who used the Navier-Stokes equation in the incompressible form, cannot talk at the same time about your intracranial pressure, which is an absolute pressure. It's just not in the equations. It is only a pressure difference. The two values are undetermined with respect to pressure. So the pressure we measure in the Navier-Stokes equation is not the same as the pressure that you're managing in patients. It's important to know that these equations do not contain absolute pressure… so where is the pressure then?

Audience responses

DR. HAROLD REKATE: Andreas, I personally am confused about that differential. Absolute pressure in your terms means what, exactly?

DR. ANDREAS LINNINGER: I hope that at the end of the presentation, we will be closer to getting there. This is a little bit professorial, but what I'm attempting to explain is that most scientists would agree that the Navier-Stokes equations contain equations that determine the relative drop of pressure at any level. So you can solve the same equations with any level that you want. But the absolute level, as you point out, you have to reference.

So where is the pressure, then, in physics? On the left, I show another version of the Navier-Stokes equation (**Fig 3**). These are only pressure differences. On the right, we have the equation for solid physics, which involves the deformation of objects. I don't want to go into the details, but all the symbols are here – symbols for stresses, deviatory stresses, displacement. More precisely, we should say deviatory stresses, which are stresses caused by displacement. But there are no pressures in the solid equations, either. There is no hydrostatic stress in the Navier-Stokes equations. So when you look for computing pressures, you would not find them in solid mechanics, either.

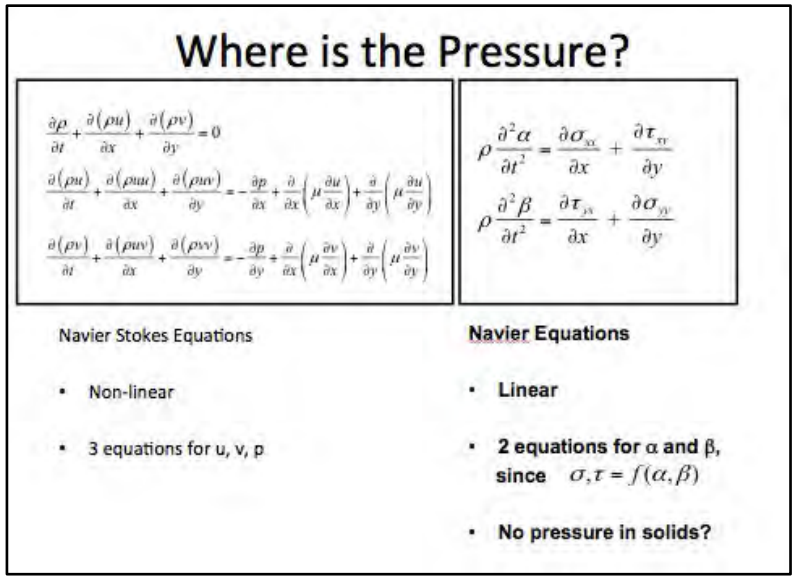

Figure 3

I don't have the slides for electric circuits, which we like a lot. Electric circuits, according to Ohm's law, current and its resistance is equal to voltage; then you can argue that voltage is like a pressure potential and the current is like a flow. Well, all electric circuit analyses do not account for potential energy nor absolute levels of potentials. This means that you can have voltage counted at any level you want; the circuit analogy also does not

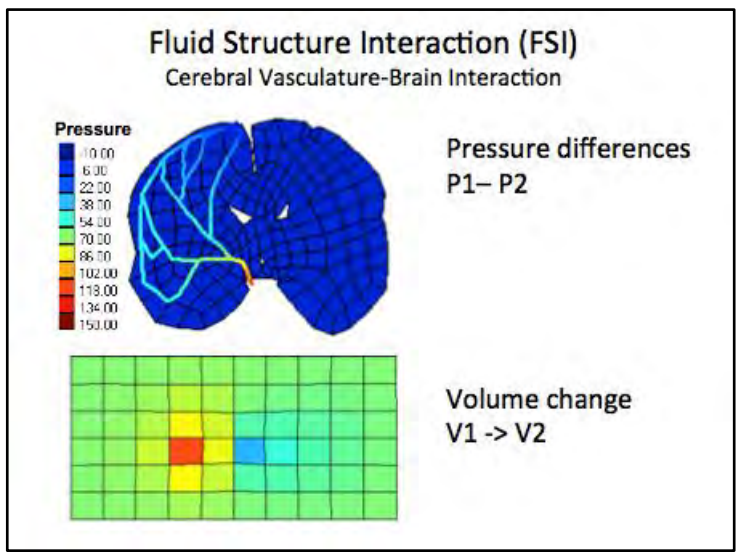

Figure 4

contain the absolute pressures we are seeking to measure. Therefore, what I observe is that I am having a hard time finding the pressure in my physics.

There is a framework in which we can account for pressures. It has to do with the compressibility of matter. Here are some simulations (**Fig 4**) that one of my students did a few years ago. This shows rectangular domain where there's a volume displacement in the center, for instance, by expanding vasculature. The emphasis here is on a difference. So the vasculature expands, and the solid around it deforms. That causes the green area on the simulation to contract and distend. It's basically mimicking the expansion of an artery embedded in CSF flow to the brain.

What is important here is that this particular model needs to account for the deformation of the space. So we have a relationship between pressure only when you have two domains which have different potentials, where the areas are able to change their volume.

The inclusion of compressibility is not a detail, but a qualitative difference in models, which do not contain the actual pressure. I have, myself, proposed models for CSF flow and intracranial pressure, in which I had not actually accounted for deformability; but all the processes we use to predict intracranial pressure without having pressure present in the equations is essentially a sort of magic trick.

We need to use what is called fluid-structure interaction, which, in this case, we account for the potential difference between the surroundings (which may be an atmospheric pressure) and the pressure elevation that occurs because of volume displacement.

So we need be careful about using physics that references the quantity we are trying to study. This leads us to two conclusions. First, we need to look at pressure differences between different compartments. Also, we need to look at the volume exchanges that those compartments experience because when volume exchange occurs, the pressures, relative to each other, are elevated.

There is a biomechanics field of research (for instance, research of distensible cubes) that looks at the pressure differences and accounts for their deformations. We, therefore, have experience in computing absolute pressures. It's not the Navier-Stokes equation, but it is in distensible cube physics.

What I am trying to impress upon you is that there is a lot of work in the literature dealing with fluid equations of incompressible Navier-Stokes, which may not really apply to hydrostatic pressure.

For the prediction of absolute pressures, what we need is the volume to pressure relationship of cervical compartments. Only when we can reference these against one another are we able to predict pressures. When we discuss volume exchanges, it is necessary to have knowledge with regard to how mass transfer occurs. For instance, if there is fluid in one compartment like the cerebral ventricles, it may be displaced in the extracellular space. Whenever we are interested in the pressure/volume relationship, it is necessary to have knowledge about the exchange of volumes between these compartments.

One item that is exchanged readily which may cause a problem in this case is water. Many of you already know from your clinical practices that managing intraventricular volume through mechanical shunting in a control strategy for managing pressure-related CSF diseases.

What I will show later is that perhaps there is also an avenue for doing a type of molecular shunting. Instead of removing the water through a mechanical device, we may be able to siphon the water out by exploiting molecular transfer processes that allow us to remove water through the natural system.

I had mentioned that there's a need to account for more than one compartment, and, ideally, these need to be spatially distributed. If you look at stress, stress is basically a great empty space. You can't compute it with compartmental models. You need to start looking at the system that is distributed in space.

So let me now view the brain, not as a simplified box, but as a complex system along with all its relevant compartments: the cerebral vasculature, which supplies the brain, the CSF domains, which support the brain and are potentially responsible for some type of clearance, and of course the parenchyma, where the brain's function lies and metabolism occurs.

The arguments I brought up regarding pressure, I think, views the brain as I just described it as a whole system, looking at the interaction between compartments in order to really capture the dynamics between each smaller system.

What we advocate is the creation of models that don't simplify the brain to the point where assumptions are made regarding relationships within the brain. Instead, we advocate for models that are anatomically faithful. We make three-dimensional models of all the compartments, which advances in imaging have allowed us to do.

My students have created some of these three-dimensional models already. We begin with a medical image or a set of medical images. We'll then let some machine-logging algorithms run over them to automatically reconstruct all the relevant compartments in 3-D: scalp, skull, CSF space, arterial tree, venous tree, gray matter, white matter – anything that you can discern is automatically converted into a three-dimensional spacial representation.

Here are six subjects (**Fig 5**). I have not included more simply because they don't fit. Basically, within a few minutes, we can convert the MRI images into a full picturization of the entire cerebral vasculature tree and all the compartments that are of interest.

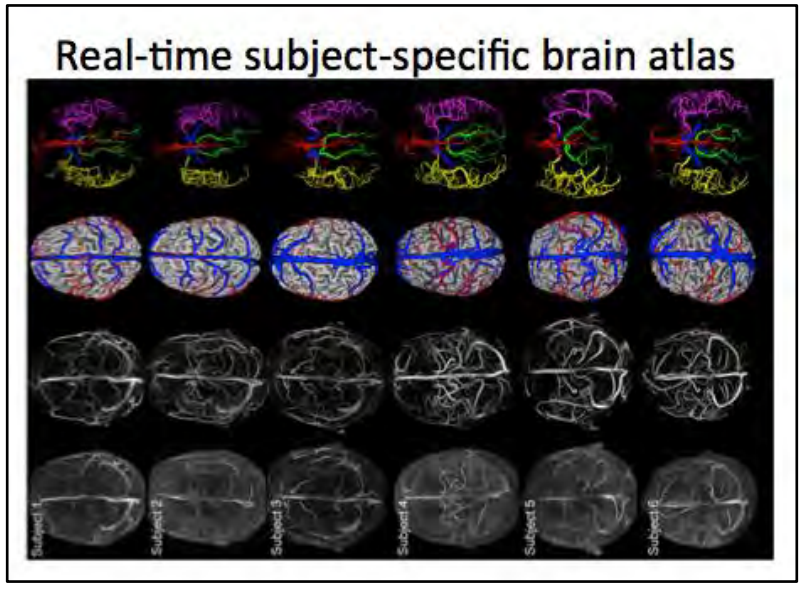

Figure 5

We are working on something like an individual brain atlas, instead of having an atlas for a standard person that's drawn by an artist. We will make a brain atlas on the fly of your brain or of your patient's brain.

Why is that important? Look at the top two images for CSF compartments (**Fig 6**).

Can you detect a difference between those two? It's very hard to tell; they look almost the same. Below them are the same images in 3-D. Now can you see a difference? (See again, **Fig 6**) Yesterday, we spoke a lot about these cuts, and the radiologists are very firm on saying, "We always look at the original images; we don't want to have any algorithm, we don't want to have any filters, we don't want to have any manipulation." But in comparing these images, it is very convincing that we just cannot see in 2-D what appears obvious in 3-D.

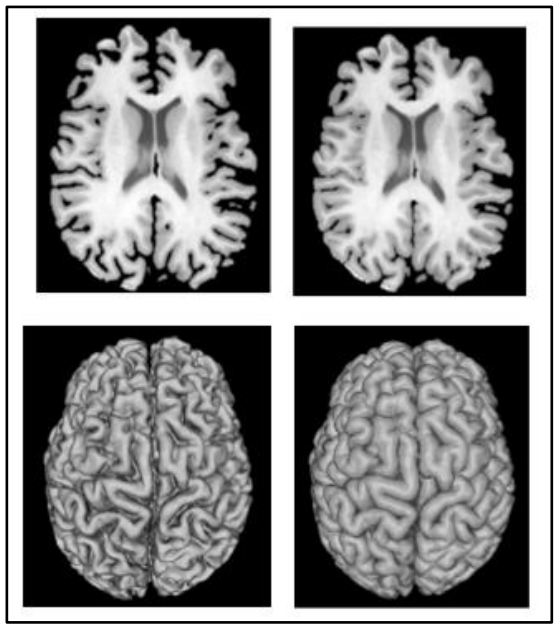

Figure 6

These 3-D images were resultant from taking a normal subject's brain and expanding it with a technique called level sets. We expand the cortex artificially by 1 mm and in 3-D, you can very clearly see the difference. But how much volume change occurs when you change the cortex by 1 mm? Does anyone have a guess?

Audience responses

AUDIENCE MEMBER: It's concentric spheres; four-thirds…

DR. LINNINGER: How many millimeters?

AUDIENCE MEMBER: Depends on the radius.

DR. LINNINGER: Okay, well what's the radius of the brain?

AUDIENCE MEMBER: …That's complex.

Presentation resumes

Yes. So what we try to do is this: we also change the ventricular size, artificially. In a normal subject, ventricular size can easily be discerned as 180 mL of change. We also changed the cortical surface by 1 mm. The difference between those two images was then constructed as a line using our imaging software. The image resolution on that construction was one pixel—just 1 mm. It's not really well seen in my slides, but the difference between those two brains was found to be 180 mL.

In other words, the expansion of the ventricles by 180 mL could easily be accommodated by the cortex expanding a very small amount— an amount that you cannot necessarily detect.

Now, I'm not saying that I know when the ventricles expand, whether the extracellular space changes, or whether the cortex is expanded. What I am saying, however, is that the arithmetic of surfaces tells us that a small expansion of the cortex may accommodate the entire expansion of the ventricles.

Why can I say that? Well, I can't say that off the image, directly. I'll have to do the math of surfaces, the level sets – a lot of bookkeeping. The image analysis together with the three-dimensional software allows us to make very precise determinations of things that otherwise are difficult to see with the naked eye, a paper and pencil, or even an electronic pencil as we saw in our analysis using the Osirix software at yesterday's meeting. So I propose that imaging enhanced with three-dimensional software for detection and genetic analysis may objectify the diagnosis and also the analysis of clinical data, similar to what we discussed yesterday.

The third compartment of importance in the brain is the parenchyma, and we are in an exciting time now regarding this compartment. Even though the brain has sparked our interest for the entire history of science, the brain parenchyma is revealing itself very slowly.

There are three relevant developments that I believe are important in the context of our research. The first one is the blood-brain barrier and aquaporin transmission channels, which presumably have a role in water exchange between the vasculature and the parenchyma. Secondly, the discovery that the lymphatic vessels, at least in the mouse, form a complete network that was originally believed to be absent in the brain. Thirdly, the emergence of a new theory about transport in perivascular spaces is proving to be important. I initially thought I'd give a whole lecture on aquaporin channels, but I defer that lecture to a review paper that I've written, if anyone is interested.[1] We looked at aquaporin and what is known about aquaporins in CSF disorders.

Aquaporin channels sit in the astrocytes. If there's a capillary, there's an astrocyte. The astrocytes' end processes ensheath the endothelial cells; so the blood-brain barrier is not only formed by the tight junctions of the endothelial cells, but it is also embedded; 98% of that surface is covered by end processes from astrocytes. On these end processes there exists these membrane proteins, aquaporins, that are especially polarized around the end. So if you have an astrocyte, all the end processes will have aquaporin.

What is interesting is that in brain injury, these aquaporin channels become dislocated; they are suddenly distributed all over the surface of the main brain, as opposed to at the end processes of the astrocytes, where they supposedly have a function. There is also an exchange between aquaporin expressed in the membrane or sitting in the cytoplasm. Thus, after injury, some of the aquaporin may not be integrated in the membrane anymore and instead it just sits around in the cytoplasm, where it may not have any function, even though it's expressed.

What does that mean for our work? The astrocytes that are adjacent to the endothelial cells may emit water, since water is capable of being transported through these aquaporin channels. It is not an active transport; it is a physical, passive transport. Again, I'm afraid to say, that pressure will come in to play. There must be a pressure gradient between the outside and the inside of the aquaporin channel in order for what to be transported. Knowing about the absolute pressure differences again becomes important. Not only does it require a pressure difference, but Starling teaches us that there is also the possibility of having oncotic pressures caused by ions, osmolytes, or substances that

are capable of changing the osmolarity. In short, these aquaporin channels cannot transport water on their own: they can only transport water based on a pressure difference.

What are the consequences of this functional placement of the aquaporins in the processes and their ability to exchange water, given some pressure difference?

Well, all data tends to point toward some kind of role in the homeostasis of water, especially in the volume of the extracellular space. There was a very interesting *Nature* paper[2] that came out relatively recently in which the extracellular space content had been very carefully measured. It shows that, in sleep, the extracellular space gets wider and the clearance is drastically enhanced, compared to the normal extracellular space. The numbers that the scientists Nedergaard and Nicholson (who basically spent his career quantifying extracellular space transport processes) show us that there's a 60% increase. Imagine that. If we have about a hundred milliliters of extracellular space, a 60% change would be 60 mL up and down, based solely on whether or not you are asleep or awake. A massive amount of volume can therefore be exchanged, according to these fundamental scientific insights. Moreover, they claim that not only is the extracellular space regulated, but there is also the possibility of having transport going across these aquaporin channels.

Nedergaard proposes a glymphatic hypothesis that states that transport through aquaporin channels travel from the arterial side of capillaries to veins. She believes, given tracer studies, that there is an active transport along the perivascular spaces; and somehow, also, she claims that in these perivascular spaces, there is transfer from the arterial to the venous side.

I also mentioned the lymphatic pathways. It has been shown in rodents that there are veins—a completely intact network of lymphatics that until now had not been known. There are several labs that have now established these pathways. These complex network again illustrates the very intricate business of water exchange between the compartments, which is important for us to understand how volume changes can occur and what pressure changes may occur in the cranium that may be clinically relevant.

There is another hypothesis concerning aquaporin involvement in transport in brain injury. Instead of being transported "magically" from the arteries to the veins, I think it is entirely possible that there are processes that are similar to the kind we know from gap junctions. The junctions between astrocytes are gap junctions and they are capable of conveying proteins extremely fast. So for instance, certain molecules can be transported much faster than by simple diffusion because the channels selectively convey them from cell one to the other.

What if you had pressure gradients in certain regions of the brain over long range, even millimeters, and the water were to go from aquaporins through these networks to sites in which there is a different osmolarity or a different pressure gradient?

This transport could occur preferentially along aquaporin and astrocytes, or it could be resultant from the fact that the membrane is permeable for water and there is a medium range transport; so the aquaporins open the gates and the extracellular space is flooded with that water.

One way or the other, there appears to be a big role for water exchange that occurs through aquaporin-mediated astrocyte transport.

What does this mean clinically? Osmolar gradients have already been used clinically; for instance, in brain injury management and edema. If you had some kind of gradient between the choroid plexus or some brain area and the CSF – if you had the difference – you could have CSF production, not only by active process but also by pressure differences. There is a big debate going on currently about whether the CSF production is mainly in the choroid plexus, or if it is distributed elsewhere. It is, at the very least, conceivable that the brain is not only exchanging water through the choroid plexus, but that there is some kind of homeostasis of water.

If you reduce the osmolarity gradients by making the blood hypo-osmolar, then production has been shown to be reduced. CSF production can be manipulated – by manitol, for instance.

What we could also conceive is that if you make the CSF hypo-osmolar, then you can draw water in by increasing the gradient. But intriguingly, we are not interested in controlling the CSF production. We are interested in controlling the CSF volume. So it's important to acknowledge these facts, but what we really want to do is to be able to control ventricular volume.

At least two labs have tried to create chronic osmotic gradients in the ventricles, presumably without changing the hydrostatic pressure. What they have seen is that the ventricles do respond to hypo-osmolar CSF: the ventricles enlarged in two different studies[34]. Thus, you may be able to create hydrocephalus chemically, without performing any mechanical deformation. We don't really want to create hydrocephalus, we want to get rid of it; so we'll need to work on the chemical manipulation to achieve that.

Thus, it seems to me that water exchange between the cerebral compartments is key for diseases and also for the management of diseases. One can sketch very naively what I have in mind, but this concept is one that will take us years to develop. The classical treatment dictates that if you start out with enlarged ventricles, what you do is you take a mechanical shunt and divert the extra fluid. This approach lowers the hydrostatic pressure, but it also has an impact on the osmolarity because doing so clears the proteins, too. This is well known.

Audience responses

DR. HAROLD REKATE: What is the classical treatment?

DR. LINNINGER: Fluid diversion through a shunt to remove CSF from the ventricles.

DR. REKATE: What do you claim that has to do with the osmolality?

DR. LINNINGER: I'm saying that removal of the fluid takes out CSF which changes the hydrostatic pressure in the ventricles, but it also removes whatever is in the ventricle. So the osmolarity of the CSF is influenced by the removal of CSF and diverting it to another area.

DR. REKATE: The amount of protein and high-molecular-weight substances in CSF is very, very, very low. I don't know that you can get it any lower than 10 mil-

liequivalents per liter. That doesn't make sense. Do you have some background for that statement—that the shunt changes the osmolarity?

DR. LINNINGER: Well, what I'm saying is that if you have, say, a full obstruction and the proteins are being kept inside the ventricles, that's one situation. Another situation occurs when you divert the fluid out. The accumulation of fluid also comes with the accumulation of proteins when you remove them with a shunt.

DR. REKATE: But unless there's selective removal of water over protein, it doesn't change the osmolarity.

DR. FRASER HENDERSON: But if you remove the CSF with protein in it, you're diluting the protein. Presumably, the protein is there, in part, as a response to degradation of cerebral tissue. We see some patients with very high proteins which develops over time in response to various metabolic functions, infections, et cetera. If you remove CSF and you create new CSF from the choroid plexus, which is very low on protein content, then, for the most part, you'll see a decrease in osmolality of the CSF.

DR. REKATE: I haven't heard that and I have tremendous doubt—

DR. LINNINGER: Let's, for the moment, say Dr. Rekate is right, as he usually is. What I'm trying to say is that within a system that is closed, if you start removing the CSF, you influence, first of all, its potential. So removing fluid changes the hydrostatic pressure; you can't help that. But also removing substances of the system will change the system.

DR. REKATE: That's definitely true in the subarachnoid space. We know that the spinal subarachnoid space can become like Jell-O if you keep it blocked. But that isn't true of the ventricles.

DR. LINNINGER: But that is not what we are discussing. We are saying that the removal of the substance from the system will influence the system. Maybe that is the common denominator on which we can all agree.

Presentation resumes

So the objective, therefore, would be to see whether we can use the exchange mechanisms in the brain to also influence water exchange in a purposeful way; so far, mechanical shunting is the only way to influence ventricular volumes.

What should we do to close the uncertainty that we have? You see the discussion already—it's very easy to find differing opinions. But what is constructively helpful to address the knowledge here?

What I would like to do is have a session where the experts come together and put together their knowledge and experience to address these issues in the context of different stimuli, similar to the discussion we just had with Dr. Rekate. For instance, if someone added a water column in an animal model, thus artificially raising the hydro-

static pressure within the system, what would happen to all the cranial compartments? Would there be a vascular compression? What would happen to the parenchyma and especially the extracellular fluid exchange? I think we should collect evidence and experiments or conduct new experiments in which we could say what trends are that occur in these compartments, through experimentation.

The next scenario that would be important to establish is exactly what happens not only to the overall system, but on the individual level in a situation of complete obstruction of an aqueduct. We must note what happens to blood flow, water exchange, as well as the water shifts between the extracellular space and the ventricles or from the cranial subarachnoidal space to the ventricles.

Another scenario has to do with the inflammation responses. If you have an injury, increased intracranial pressure is often observed. What are the explanations for this intracranial pressure rise? Before we create models, it would be nice to have a dialogue so we can establish with which observations we are concerned and we will then be able to state them, without explaining them. The dialogue should also not delve immediately into opinions, instead we will discuss what is it that we observe, without judgment.

A final scenario to consider is osmolarity change. I spoke about the hypertonic blood therapy, hypotonic blood therapy or hypertonic lateral ventricle infusion. I think establishing what occurs in the brain dynamically as a function of space and time would help us understand. Right now, I cannot find enough evidence to piece together all these scenarios, at least, from a research point of view.

So I've argued for the need for pressure and volume relationships. Our lab has tried to make a contribution by developing a pressure-volume sensor. Here are some results from in vitro experiments (**Fig 7**) that show all the scenarios of relevance: normal pressure hydrocephalus, CSF clearance, flow through slit ven-

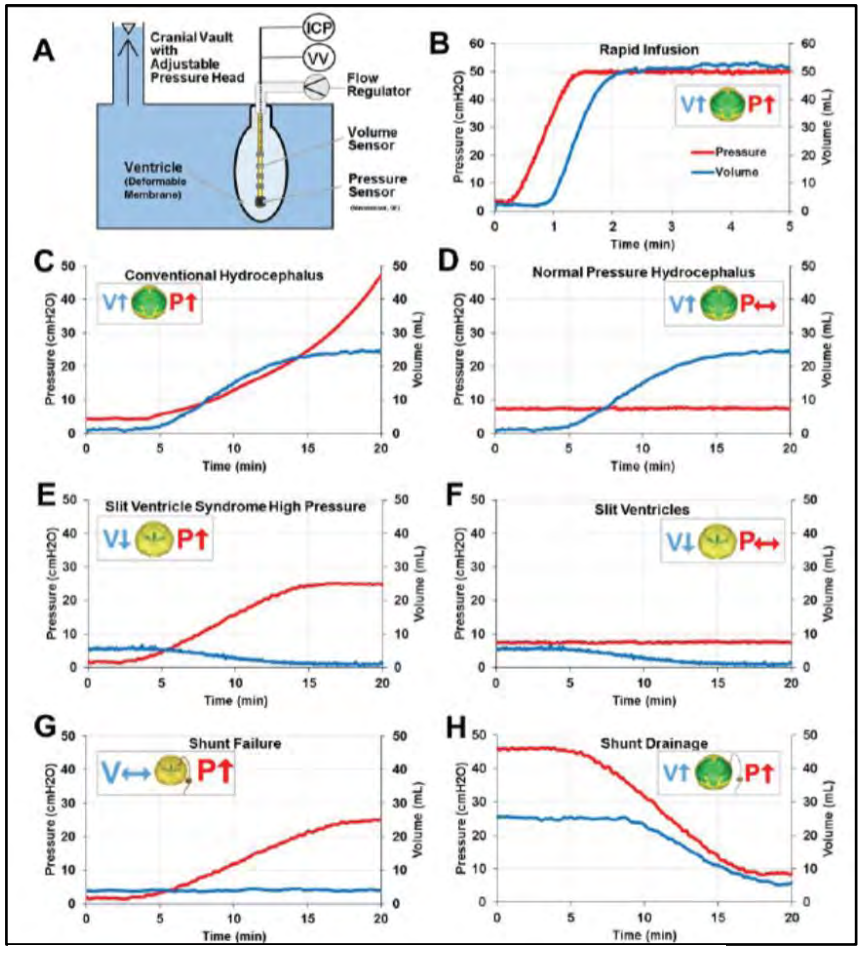

Figure 7

tricles, shunt failure, et cetera. Essentially, the volume-pressure sensor, which emulates a small ventricular expansion in an in vitro setting, is capable of tracking volume and pressure changes that may occur in different clinical scenarios.

We have also developed pre-clinical rat sensors and rabbit sensors that, when implanted, can simultaneously track intracranial pressure and ventricular volume, including pulse pressures. I believe that, before we make those pressures available chronically and for research purposes, we must know how volume and pressures develop in the brain so that we can form adequate hypotheses about the fluid exchange in the cerebral compartments.

Finally, we are also investigating the water exchange that presumably occurs at the cellular level. So instead of looking at only the expression of aquaporins, we have created a device that we hope will help to measure the flux across an astrocyte.

We have created a microfluidic device that separates the astrocyte soma from the processes. We also now have the ability to apply an osmolarity gradient on both sides, the side of the soma and the side of the process.

We would like to use a quenching experiment with fluorescein to measure the amount of water that is actually transported in the particular function of osmolarity gradient. This will help establish whether or not astrocytes are able to carry water fluxes and to quantify these water fluxes between single astrocytes and maybe networks. We have some preliminary figures to show that astrocytes are really separated from the soma to the end process. (**Fig 8**)

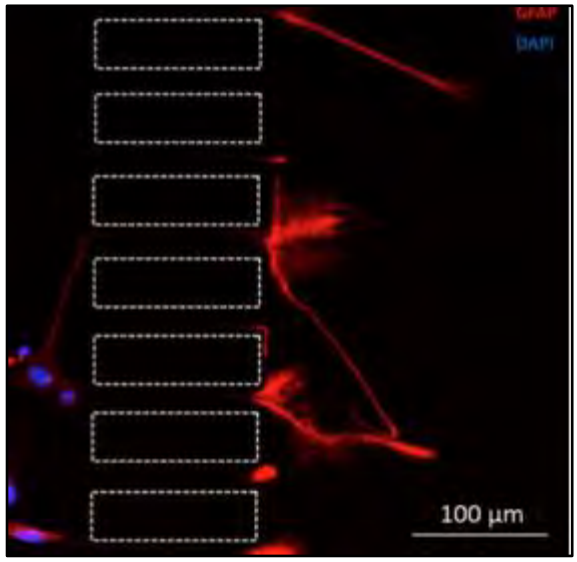

Figure 8 – The microfluidic device induced astrocyte polarization separating the soma (right) from the endfoot processes (left)

Perhaps, then, these are our first steps towards understanding the whole brain as a system of connected compartments when we construct a compartmental model of brain, CSF and vasculature. We include vasculature, perivascular spaces, and tissue in the context of a balance equation in order to create this molecular model of the brain.

We have actual mouse data (**Fig 9**) showing a soma of neural cells and endothelial cells; so basically, our model has an inventory of every single cell. The model illustrates capillaries—every single capillary in the mouse cortex. The model uses predictions that are based on the Starling forces that I had spoken about earlier. It shows that there are areas of reabsorption and generation of water.

Within the system, the exchange of fluid is not only driven by blood flow; we have allowed the blood-brain barrier to be open to water transport using aquaporin channels. It would show that we have a path in here in which some of the microcirculation is able to filter water out and some it able to be reabsorbed. It is imaginable that in injury, the balance becomes shifted and suddenly we will have a surplus of production, leading to mis-arrangement between the volume of water.

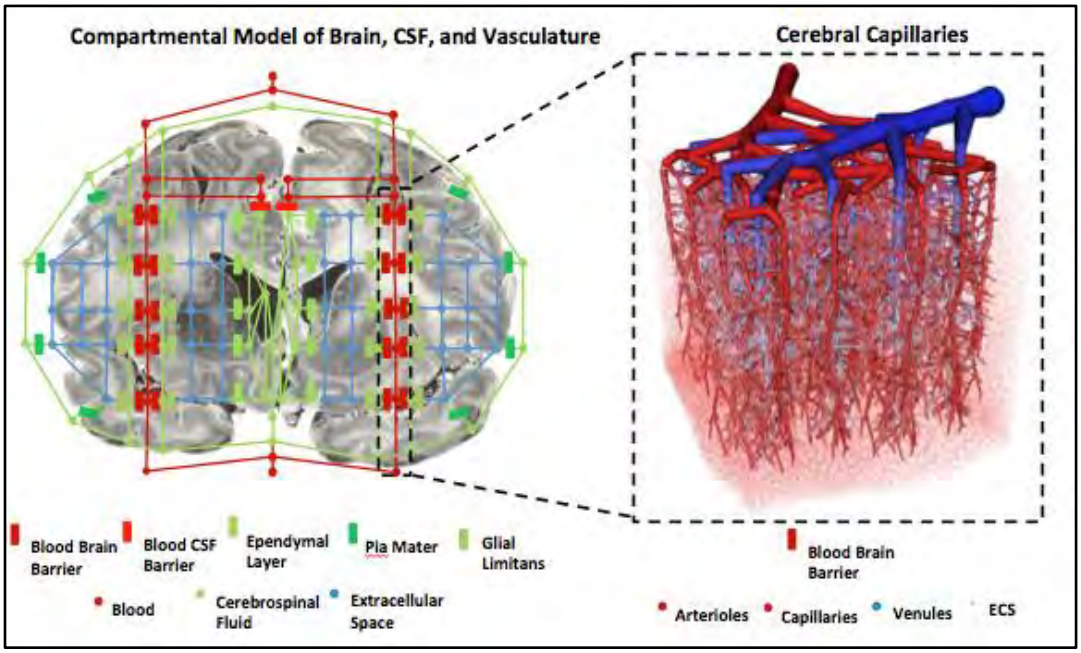

Figure 9

In conclusion, the hydrostatic pressure that is important for the change of cerebral compartment size, like ventricles, is a very tricky quantity. The many models that are presented use the compliance relationship as input, but these do not really predict the intracranial pressure rise, they are just reflective of what we are entering into the equations. What we need is a characterization of the fluid exchange and also the deformation between all brain compartments, which require a distributed model. We have also advocated for the creation of 3-D models that area as faithful to the anatomy of the brain as possible.

So in you experiments or in your models with the engineers with whom you work, I hope that you will ask for pressure and volume; how the pressure and volume are accounted for in your systems. I also hope we have a chance to start working towards establishing two models that, for instance, are capable of predicting why intracranial pressure can rise in an injury, or why it can rise in obstructive scenarios, to really predict or reproduce those phenomena that occur in nature.

I thank you for giving me the chance to share my own ignorance about pressure and volume and I'm happy to entertain your questions.

Discussion following presentation

DR. SUNIL PATEL: Forgive my ignorance. How does pulsatility of the pressure in the brain affect all of the systems that you've described? Are you planning to look at that?

DR. LINNINGER: I think pulsatility is a very important example of showing the need for qualitatively having deformation. If the vasculature was rigid, then you could not have any pulsation that causes CSF to move, because the entire impulse of the blood

would be contained inside of the vasculature. So whether you're interested in deformations or not, the pulsations that cause the CSF to move, again, needs this full structure interaction. Or, for instance, the motion of CSF into the spine in asystole, we don't know exactly the displacement and the deformation that occur in the spine.

But one thing is clear: we know from different laboratories that measure this, that about 1 to 2 cc's of CSF are descending into the spine. There must be some give in the spinal compartment to allow for that fluid. So we, again, infer that the deformation of the spine or the displacement of venous blood—that some kind of displacement is capable of permitting that.

If you use the Navier-Stokes equations—as many people do when studying CSF dynamics— you can neither study deformation nor displacement. The investigator will have to use fluid structure interaction, which, for engineers, is often very painful because there are no codes available. So the paper will generally start by stating that fluid structure interaction studies would be interesting, but the effects are small. In actuality, the effects are not small, but they're qualitatively different.

Deformations and pulsations go hand-in-hand. If you don't have a deformation, you can't really work with a dynamically moving system. It is qualitatively important, not a question of predictive position. It is a question of faithfulness to the proper physics. So pulsations are absolutely an important point.

DR. HENDERSON: I think that the distensibility of the lumbar cistern may be greater than we previously thought. We see in a lot of patients, especially those with genetic conditions, that they develop very wide distention of the lumbar cisterns. This could really hurt your calculations, correct?

DR. LINNINGER: Well, I don't show it now, but I have a paper that will come out next year on cerebrospinal fluid mechanics and its coupling to cerebral vascular dynamics.

What we will show is that we measure the CSF flow and pulsation in the spinal compartment, accounting for deformation in the lumbar region. BY using that hypothesis, we were able to produce a prediction of the 3-D flow field. When we compared the flow field that we have measured with the flow field that we have predicted under the assumption of deformation of the lumbar region, we found that the curves look similar in space and time. We hypothesized that the deformation of the lumbar region is capable of producing those flows that we see clinically of CSF moving up and down the spinal compartment. It is not proof: it just shows that it is possible that the mechanism may work that way.

The point is, if you had a model in which the spinal CSF compartment was completely open, you can do anything you want by changing the boundary conditions; but if it is closed, you would not be able to get a drop of CSF into the spinal column, so it had to be deformed.

DR. MARK LUCIANO: First of all, wonderful talk.

We have been looking at the change of impedance and the resistance of the cervicomedullary junction in fluid flow, but also its relationship to deformation of the tonsils, the brainstem and pulsatile changes.

I'm sensing that some of your analysis can be useful, not just for looking at the cranial and spinal differences, but also when looking at the deformation at the cervicomedullary junction and pulsatile deformation. What we need to find out is how important is that pulsatile deformation? Does it, for example, progress over time? Or does it, over perhaps one million heartbeats, create more and more deformation?

So the kinds of forces on that tissue, with interaction with the fluid flow, is a key issue in Chiari malformation, I think.

DR. LINNINGER: "The brain is a passive sponge." I believe there's no real evidence this is true. The brain has, in contrast, poor elasticity, which is the physics of sediments like of aquifers. They don't have veins and they don't have capillaries and they don't have aquaporin channels.

The compressibility of the brain tissue in vivo is different than when measured mechanically. If it is cut out and measured with mechanical devices, it's not the same brain; it needs to be studied in vivo.

I suspect that the deformation of the brain has a lot to do with shifting water, as it does with deformation. I think that to insist that the brain is a "passive sponge" that can be submitted to poor elasticity theory because it has always been that way since the '40s is questionable. I think the brain is something that, when you compress it, you may be pushing fluid into the capillary bed. We need to entertain the possibility of having models that are able to address that, both experimentally and in our mind-set.

The application of numbers and throwing some complex mathematics on someone should never obfuscate the big picture. Unfortunately, I had to use a few equations, but I think, at the level that we are speaking, it doesn't make a difference whether you're a physician or an engineer. We should be able to talk about the physics without the detail of the equations.

Is the brain about to be dried by compression? Yes or no? This is why I believe the theory that the brain being a passive sponge is a myth. What you're saying is exactly right.

So I challenge you to be bold with changing this. You don't have to solve the equations, but challenge your engineers and say, "Look, can you dry the brain? Can you push fluid inside? Can I change, for instance, blood flow? Your work showed a change in the ventricular area of ischemia. Is a model capable of showing that? Not the stresses in the brain tissue, but the change in resistance to blood flow. This theory doesn't allow you to do that; so what information do you expect it to predict?"

DR. DONLIN LONG: Andreas, that was superbly done.

It occurs to me that almost everything you say is appropriate to studying brain edema, as well. Is that a part of your project?

DR. LINNINGER: Well, it is my hope that it's recognized that the work is applicable. As engineers, we are pragmatic. We want to build a bridge and not at the same time, a building; but if that bridge helps to connect buildings, it's fine.

The understanding of water exchange is a fundamental question. A fundamental understanding that I think we can use, Dorothy, for raising the profile of hydrocephalus research.

Hydrocephalus research and water exchange is not distinct to hydrocephalus or syrinx formation. It is the key to all brain injury, where water accumulation cause problems in traumatic brain injury, non-traumatic brain injury, edema, et cetera. It's the same brain. We in the CSF community are most informed about the changes that occur.

Even neuroscience is more interested in the expression of proteins. For example, the experiment that we propose by measuring the water flux is very unlikely to be done in neuroscience because they claim that when they find the protein and perform the knockout, they know that it involves an aquaporin channel and that channel somehow transports water—further explanation of mechanisms is not added.

What you want for your patients and we want as engineers is to quantify the flux. Is this a significant flux? Is something out-of-whack, causing accumulation? Could the flux somehow be harnessed for removing water using a pharmacological intervention?

We submitted a proposal in which we asked whether or not we could use aquaporin regulation, up or down, to influence reabsorption. Now, this is, as of yet, a very speculative proposal. However, it has the chance to do something completely new, and this is where we should focus our energy.

If we advocate why hydrocephalus research is important, it's not only because we want to help those patients that you are so passionately treating, but it allows us to address the fundamental questions of what happens in brain injury. It is the same physics of water exchange that occurs maybe based on oncotic differences cause by the proteins that are extravasated in, say, vasogenic edema from injury, that's causing the aquaporin channels to be moved by cell rupture that spills out the proteins inside the cells and the extracellular space, creating an elevation of osmolarity.

These fundamental mechanisms are what our community is apt to study and deliver to a wider community in brain injury. Absolutely.

DR. LONG: This is really a throwback to 60-year-old research, but you might be interested in knowing because even someone from years ago might know that the shark brain does not respond to injury. The astrocytes do not swell.

I did this with Igor Klatzo back in the early '60s and we spent a great deal of time studying the blood-brain barrier in the shark. We gave up when the tight junction was discovered.

But in the shark, the capillaries only go through the bodies of astrocytes, and the brain does not respond to injury. You can't see anything that looks like the brain has been injured. That might be an animal that may give some keys to what's happening in other species.

DR. LINNINGER: I will definitely look that up, if you don't mind sharing the reference with me.

DR. LONG: I will.

DR. LINNINGER: Thank you.

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9. Intracranial Hypotension: What We Know and What We Know We Don't Know

DR. MARK LUCIANO, MD, PHD

Thank you. It is quite difficult to follow such a high-level talk. I admit to being confused about all this; and after hearing your talk, I admit that I am still confused, but now that confusion is at a much higher level. I am also experiencing a little trepidation in terms of my own presentation in the sense that it poses more of a question than a solution and that it is more of a review than presentation of new data. Often if I have an epiphany or a new idea, the first thing I suspect is that 30 percent of the clinicians and neurosurgeons here already know about this and it may be old news. So if this is truly a review for this group, then I hope it is at least a good review.

I think I am approaching this topic with a different emphasis and in a way that, at least for me, is new. I don't have any disclosures about this; but I do have an acknowledgement that I would like to make to Linda Gray, a neuroradiologist in Duke.

I went down to see her and see how she treats people, who travel long distances. Patients travel from as far as the West Coast to see her. She specializes in seeing patients that have CSF leaks and hypotension. These patients can be very difficult to diagnose, they have severe symptoms, and they are often very difficult to treat. However, when you do find those leaks and successfully treat them, patients can experience dramatic improvements that they otherwise would not if those steps had not been taken. It was very moving for me to visit Dr. Gray, to see these patients and observe how they were being treated.

As a result of my visit, I also have a few slides and case studies from her. Because of my recent move to Johns Hopkins, I do not have all the access to some of my older cases and these cases from Dr. Gray have helped supplement my material. I began to look at this issue more and more while I was back in Cleveland; and understandably, I found that the more I looked for hints of hypotension and CSF leak, the more I would find them. I mention this because I think that is important.

I will get started with something we all know extremely well: as there is with lumbar punctures and anything that causes a leak in the lower spine, if there is lumbar drainage, there is the potential for a Chiari malformation, even a severely symptomatic Chiari malformation. This is all well known. We also know that this occurred and was published primarily in a time where very little in the way of resistance or valves placed into the systems, so there might have been overdrainage in a lumbar shunt just because of that as well. We might also say that this happened more in the pediatric populations, perhaps because the brains in children are fuller. As we age, there is more CSF space and the posterior fossa becomes less crowded naturally. Therefore, we see more of this acquired Chiari in the younger populations.

So we may start to believe that since we know about this phenomenon and it is fairly rare, we need not think about it as much. However, there are cases that will gently remind us. This is a child that had hydrocephalus with a very complex treatment plan

with multiple shunts. This particular child **(Fig 1)** came to us having had, I think, something like eight to ten operations, including VP and lumbar shunts.

We looked at the image and noted that things seem very tight in the posterior fossa. What was typical in this child is that he was very sensitive. If the shunt blocked up, he became comatose, though the ventricles were changed very little. He was clearly extremely sensitive to small changes in pressure or volume and that may be because his posterior fossa was also a bit tight.

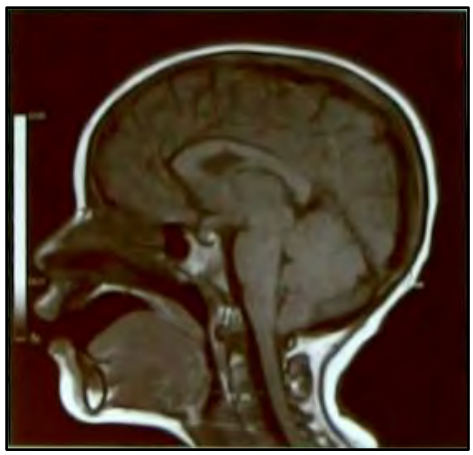

Figure 1

Looking back at his MRI just before the lumbar shunt was put in (**Fig 2**), we saw something that was surprising but perhaps should not have been so surprising. We were able to see just how much CSF space there was and the lack of crowding there was before any shunt was placed. Though, we should remember that he is shunted from above as well.

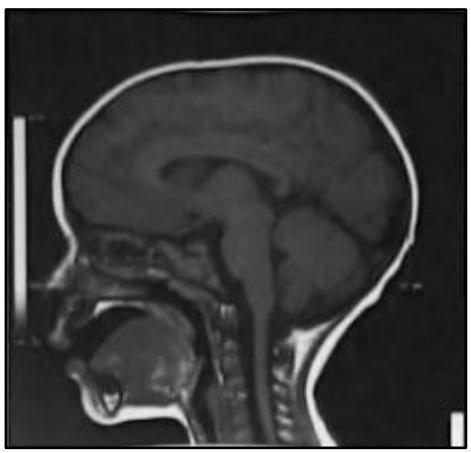

Figure 2

This made us realize that the developed Chiari was really just adding to a problem here. It was likely making him much more sensitive and causing symptoms on its own. So it is not rocket science; all we did was tie off the shunt from below— actually, we ended up removing it eventually— and the Chiari malformation did tend towards normalization (**Fig 3**). Afterwards, he became much more tolerant of CSF drainage; he did not become comatose if his drainage was lowered as he had been known to do previously. I do believe that the sensitivity that he had in his treatment of hydrocephalus was, in part, due to the posterior fossa and, of course, to that lumbar shunt.

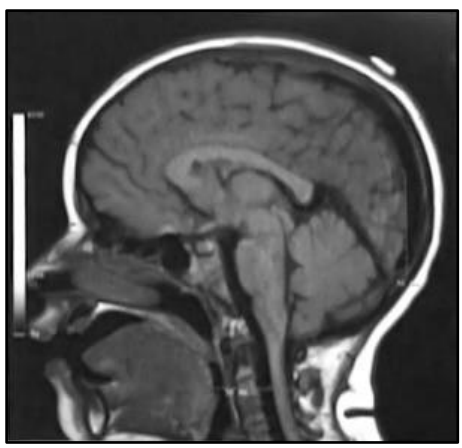

Figure 3

This tells us, then, that lumbar shunting can be a problem, especially if there is a crowded posterior fossa; lumbar shunting seems as if it can make a problem worse or make treating other issues like hydrocephalus even more difficult. So when we go back to the outpatient clinic and we are screening patients with Chiari, all of us know that we should keep an eye out for CSF leaks. We do so by finding out about postural headaches and see if they have obvious symptoms of positional problems. We also know from Dr. Rowe's previous work that there are many reasons to have orthostatic headaches and symptoms; CSF leak, of course,

can be one of them.

We also know that we should look at the head MRIs. If we have an MRI of the head and not just the spine we may see subdural hematomas or hygromas that are slightly enlarged. If we have MRI with dural enhancement, we might also find that the dura is enhanced. These are the typical things that I think most people in the clinic are watching out for, both clinically and radiologically.

There are other anatomical warnings that we could be looking for with a little bit more hypersensitivity, and the acronym is SEEPS. These warnings include: subdurals; dural enhancement; engorgement of the veins that occurs throughout the venous sinuses and also the epidural veins of the neck, which can cause some symptoms as well; pituitary hyperemia, an enlargement of the pituitary that can be seen on the coronal and sagittal views; and, of course, the general phenomena of sagging of the brain.

Sagging of the brain can be obvious or not so obvious— so I would like to discuss what that can look like just a little bit more. The first iteration of this is the cerebellar tonsillar descent, posterior fossa crowding. Most of the patients that come to us for evaluation with Chiari malformation have this morphology, and we are not surprised if we see this so it does not necessarily evoke the idea of this case of a sagging brain. Sagging brain may also be observed when the optic chiasm is displaced downward and the chiasmatic cisterns are compressed. There is also a descent of the brainstem where the opening of the aqueduct is actually below the incisura; it is actually, in a sense, in the posterior fossa. And we may also observe a general decreased size in the basal cisterns. These are all changes that we can observe; but it is important to say that we do not always see them, for one part, because we are not always looking for them or we do not have those images available because they do not always exist with CSF leaks.

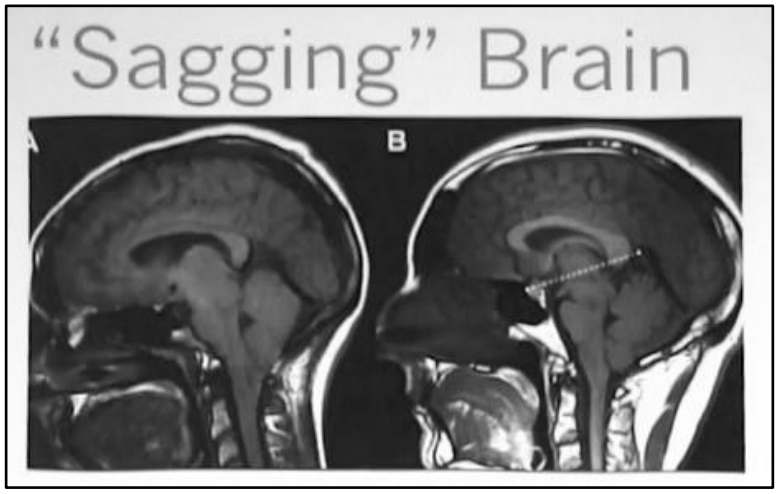

Figure 4

Here are pictures (**Fig 4**) of what may be considered the typical sagging brain. We see here examples of the tightness in the posterior fossa, the closed cisterns, the Chiari malformation. On the picture on the right, we see the line between the tentorium and the anterior clinoid indicating that the brainstem is actually lower. These are findings that are not so subtle; but we see a lot of these symptoms or a lot of these morphological features in the posterior fossa also with our Chiari patients. We do not want to miss the other features that may indicate a CSF leak or hypotension. If you look at the coronal and the T2 in the image on the left (**Fig 5a**), it is quite obvious the hygromas that have evolved, the smaller ventricles, the enlarged pituitary; and on the right (**Fig 5b**) I have included a diagram of these same findings showing increased venous sinuses, the pitui-

tary, smaller ventricles, and those hygromas, which do not have to be large subdurals but may just be expanded CSF spaces with little or no mass effect. We have to be sensitive to look for those findings, or else we will not see them.

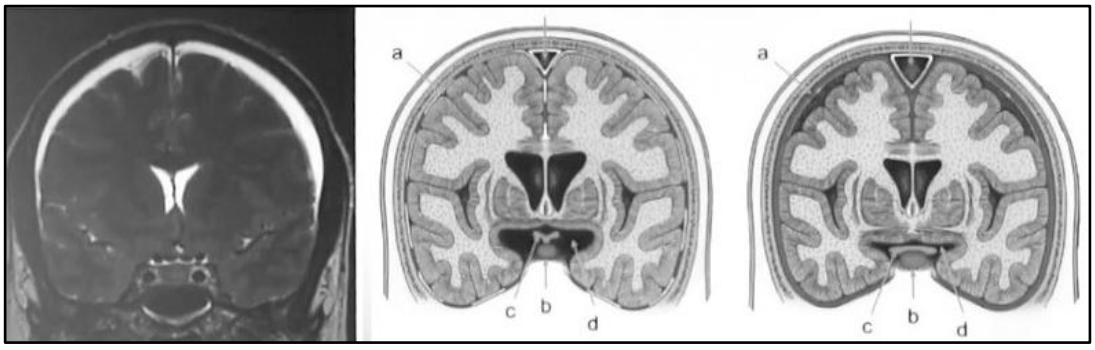

Figure 5a

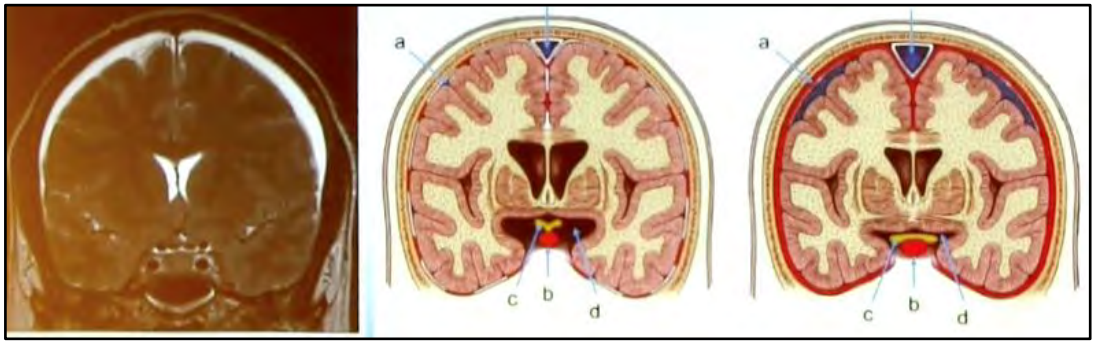

Figure 5b

So what causes CSF leaks and hypovolemia? The obvious is what we have already been reviewing: overdrainage with a shunt. The second, of course, is trauma of any kind. For instance, a car accident or a brachial plexus avulsion can cause a CSF leak. But there are also more subtle procedures that can be the culprit such as lumbar punctures and epidural catheters that have gone wrong or gone too deep. Cranial and spinal surgeries may also be at fault. Just as a note, I will be focusing more on the occult and the spinal CSF leak than the cranial leaks in the remainder of my presentation.

The next cause is where we start to get a little bit murkier, in that, sometimes there is a history in these patients of very minor trauma, one example maybe being a chiropractic encounter. This history is detected about one third of the time and we are forced to ask whether or not this somehow caused a CSF leak. Often, especially in the thoracic regions we might see spurs or discs which also cause a ventricle CSF leak. And as we get down to these difficult to discover kinds of causes, we find that they may or may not be able to be identified. Sometimes CSF leaks are just what we would call spontaneous intracranial hypotension or an occult CSF leak.

What I am trying to emphasize by going through all of this is that we know about the larger and more observed cases; but there is a question about how many times we might have smaller, more subtle changes that we are missing. Instead, we can be more vigilant by focusing on what we call spontaneous intracranial hypertension. These might

be caused by a potential minor trauma that may or may not be in the history or even a disc which may have been previously determined to be clinically insignificant, with no mass effect but may actually be causing an undetected CSF leak. We may see more spontaneous leaks in a proportion of patients who have connective tissue disorders. We also know the reverse to be true: people with spontaneous intracranial hypotension do have increased risk of connective tissue disorders. These may also result as a combination of minor trauma or a disc and connective tissue disorder. If we have a person with connective tissue disorders, it might take a minor injury to cause a CSF leak, which may or may not then present as a sagging brain.

The pathophysiology of spontaneous CSF leaks is not likely due to a hyperactivity of an absorption system or a decreased CSF production. It is likely due to that loss of CSF volume. You can think of it in a static fashion in terms of the sagging brain pulling on cranial nerves and compressing; but you can also think of it in a more dynamic fashion in regards to pulsatility and the fact that the spinal canal has much more compliance and there is, in a sense, a change in the compliance of the cranial versus the spinal spaces with more pulsatile movements. So these kinds of factors – pulsatility, static changes and movement of the brain – can all cause symptoms with CSF hypotension.

In terms of prevalence, it is difficult to determine the prevalence of something that we cannot always identify; but we can find out how many times it is actually being discovered. The prevalence is approximately 1 in 50,000 in a general community of people. It has been found that incidence is 5 in 100,000 in an Emergency Room visit per year. Those sound like low numbers, but actually, that roughly translates into a population that we will encounter in our clinics.

The ratio of spontaneous CSF leak is similar to those ratios we see in other conditions such as pseudotumor or Chiari, with a larger number of patients being female. This is found in all ages, but it seems to peak at 30 to 50 years. Of course, again, this data is based only off the cases that have been discovered.

This is just a bit of a side note but I thought it would be important or interesting to note that in this study[1], for example, they looked at a large number of patients and found a general overall CSF leak where there was surgery of about eight percent. But when one considers risk factors like smoking, diabetes and hypertension, that CSF leak risk went up 33 to 44 times. The risk of CSF leak changes with systemic factors of healing, CSF dynamics, and to a great extent, connective tissue disorders. So if we are to say that CSF leaks happen very infrequently, it really is important to consider the various states of the patients on whom we are operating. The risks can be quite high, even with minor traumas or minor pinholes following surgery, as in this study.

So how does spontaneous intracranial hypotension present? We have been talking about headaches and orthostatic headaches and it would be great to hear more about differentiating them from other orthostatic symptoms. However, it is also important to know that over time when it becomes a chronic headache, it can switch from an orthostatic pattern to one that is pretty lingering and constant. So when we take our history, we have to – if we can – tease apart early presentation from what the patient may be experiencing months or years down the line, because there are many patients that have this kind CSF leak that may no longer have an orthostatic component to their symptoms, but more steady and constant. It can be considered exertional. It happens more frequently at the end of the day; so that is kind of a vague way of saying that there may be some level

of positionality to it as well, though not as direct. These headaches are often either occipital, frontal, or both; they are rarely unilateral, usually bilateral, but they can often involve the occipital region. They may involve the neck and the interscapular area. Patients may feel like a throbbing or pressure-type pain. Sneezing, coughing and head movement exacerbate the headaches. We can see, then, that there is some overlap you see in the symptomatology. Again, these are patients we are often evaluating for Chiari malformation, so this is something that has similar symptoms and can produce some of the same morphological features that we are trying to evaluate and tease apart in Chiari.

It is also important to note that sometimes these patients present with bona fide leaks that are established either by anatomy, sagging of the brain, dural enhancement, or by clear positional symptomology, but they do not have headaches. So headaches are not always present and you cannot depend on them all the time.

You also cannot depend on high or low pressures. Many of these patients have pressures below six centimeters of water; but 25 percent of them have entirely normal pressure.

Other symptoms of spontaneous intracranial hypotension include neck and interscapular pain, and hearing loss, likely due to the communication with the endolymph and the fluid in the ear, as opposed to perhaps traction on the nerves. There is also nausea and vomiting and a host of other symptoms that have been reported based, most likely, on traction on the pituitary stalk and nerves. For example, bibrachial amyotrophy; patients get weakness and numbness in their arms. This may be due to the large engorgement of the veins in the cervical region associated with hypotension.

There are various causes and physiological changes that occur with hypotension, and they cause a variety of symptoms. It is, I think, good to keep that in mind if you see a patient with a presentation on this spectrum.

The pure definition[2] of all this is broken into three parts. Number one: headache fulfills Criterion 3 – which means there is headache. Number two: there is either low pressure or some evidence of CSF leak. And finally, number three: there is some connection between the leak and the headache; either the leak and headache occurred at the same time if you have access to that sort of information or the headache led to an investigation that found a CSF leak. So you see, the definition is pretty nonspecific if you look in the diagnostic codes.

Let me provide a little diagnostic overview because this has all been changing quite a bit in the last ten years – there are multiple modes and they can get a little confusing as to what should be used and what the sensitivities are.

The first option we have is the plain cranial MRI that we talked about with gadolinium, looking for those SEEPS features with enhancements, so forth; but we also know that that – and I will show an example – is not very sensitive.

A cisternogram has been widely used. We all know that if you inject tracer through a lumbar injection, you may see an area of leak. It is not good at all for localization but can often identify some leak and some conditions of higher flow.

A myelogram can give some good detail and sometimes find a leak as well, especially with digital subtraction myelogram. There is also the CT myelogram, which is probably the most frequent type of study. After injection into the lumbar spine, a CT scan is done and may show the exact localization of the leak; but it remains also quite insensitive. There are two other kinds of problems related to the CT myelogram. The

first is that it may not identify a slow leak; if the leak only occurs in episodes or occurs too infrequently, the CT scan may not catch it. In contrast, there may be a fast leak. The fast leak is problematic because if the patient is shuffled off to the CT suite and the leak is dissipating quickly, that tracer may be long gone after another hour when they get their CT scan. So a CT after myelogram can be quite insensitive on its own.

Other types of post-myelogram CTs have been described where you, in a sense, do the myelogram right on the CT table in an angiograph sort of fashion, called a dynamic rapid imaging. Often you can also add some volume, as Dr. Gray does over at Duke. She adds some volume of fluid, increasing the pressure just before she does the dye injection. That increases the sensitivity.

There have been advances in the MRI diagnosis as well. First of all, we have what we call a CSF leak protocol, in which a very heavy, weighted T2 image gives you what looks like a myelogram of the spine. This was very exciting because it was a noninvasive way doing getting this information – a very nice way of screening. Unfortunately, it also remains insensitive to really seeing CSF leaks; it can show the paraspinal cysts and areas that may be suspicious, but it cannot help very much in finding the leaks in most cases. To try and improve this, there has been gadolinium injection with saline infusion. I will talk a little bit about these and their relative sensitivity.

First, I want to say a few words about the basic image, looking for the sagging brain and using radionuclide studies. This was a study from 2014[3] in which 250 patients who had suspected symptoms of intracranial hypotension underwent radionuclide studies. The investigators also obtained the MRI cranial or head MRI images and looked for the sagging brain. They indeed found a leak in about 74 percent of these patients on the cisternogram, but only in 13 percent of the brain did they find any evidence of sagging of the brain, and they were looking for evidence of this with intent. So, as much as we might like, sagging of the brain is not as constant a feature— it is not as sensitive a test as we might like.

In addition, when they did see sagging, it was not necessarily associated with the patients in which they saw CSF leaks, which also cast some doubt over the accuracy and sensitivity of the cisternogram. They only saw one case of dural enhancement; since we use dural enhancement all the time as an indicator, we must accept that it, too, may be very insensitive.

So what about the mainstay of CT myelogram and MR myelograms? This was a study of 24 patients[4] — if you notice, even these studies have very few patients in them. The patients included in this study had clinical and MRI craniospinal criteria for spontaneous hypotension. On the left you (**Fig 6**) see a CT myelogram showing the enhanced CSF around the spinal cord; and on the right you see the MR gadolinium injection. In the gadolinium injection images, you can observe a fluid leak, a diffuse area on the left side of the top panel and on the bottom panel you can observe a diffuse area on the right. It took an MRI with

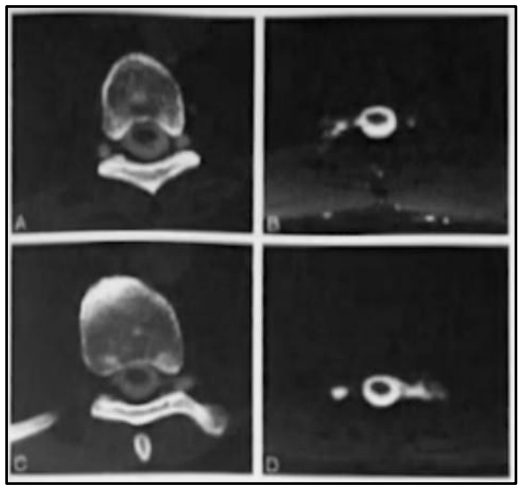

Figure 6

a gadolinium injection to show that there was a leak that could not be seen on the CT myelogram.

So in this study— again, admittedly done with a small number of patients— they detected three CSF leaks, and localized them with a CT myelogram. They detected those same three and then six more when they used the MRI technique. And that is better; but you notice the green bar on the right (**Fig 7**), that 63 percent of the leaks they still could not identify, even in these patients who had definitive symptoms and other evidence of a CSF leak. That means that there are still a lot of patients that we know, either anatomically or symptomatically, have CSF leaks that we are unable to determine how to treat since we cannot find out where the real problem is localized.

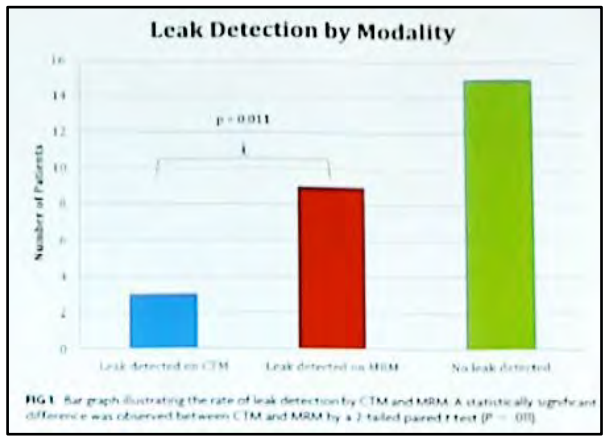

Figure 7

Another study[5] showed similar sensitivity and lack thereof with MRI gadolinium studies. They developed this complicated algorithm, placing gadolinium MRI injections and myelograms higher up in their protocol and then later on in the protocol doing CT myelograms and other dynamic studies— all to try and find an elusive leak.

This is a study from 2015[6] that discussed the method of injection— one third of the total volume of fluid, probably 70 cc's— I do not have the rate here. This team had an infusion of fluid that they gave before the injection of the gadolinium for MR. In this case, they did find increased sensitivity to the leaks. One of their comments was particularly enlightening:

> "Dynamic [CT myelogram (CTM)] provides increased temporal and spatial resolutions, which improve the identification in cases of high-flow leakage. Similarly, [contrast-enhanced MR myelography (CEMRM)] appears to be more sensitive than conventional CTM, enabling improved identification of subtle CSF leaks."

So the concepts from these studies are envisioned as being complementary. These papers provide just another example of how hard it can be to find these leaks because there may be an issue with high-flow versus low-flow; different imaging methods may be used to identify one over the other.

Here is an image from the last group's study (**Fig 8**). The lower panel on the right, we can observe fluid coming off that cannot be detected from what looks like a pretty clean, sealed-off cyst on the CT myelogram on the left.

So in summation, many leaks are missed, there are problems with fast and slow leaks, and there are different techniques with varying sensitivities. Dynamic CTM and digital subtraction myelogram are good for the fast leaks, and perhaps the MRI gadolinium injections and higher pressures may be more useful for the slow leaks.

But once we find these leaks, how do we treat spontaneous intracranial hypotension? It is best to begin conservatively, of course, with bed rest and hydration. Sometimes this is successful, but often it is not. The next treatment level involves caffeine and steroids to, again, often unsatisfactory results. Blood patching is done empirically once, twice, sometimes three times. With this method, there are occasionally problems with rebound hypertension; if you do fix the hypotension, the pressure can build up and burst what had been sealed off. This rebound phenomenon can be decreased with Diamox.

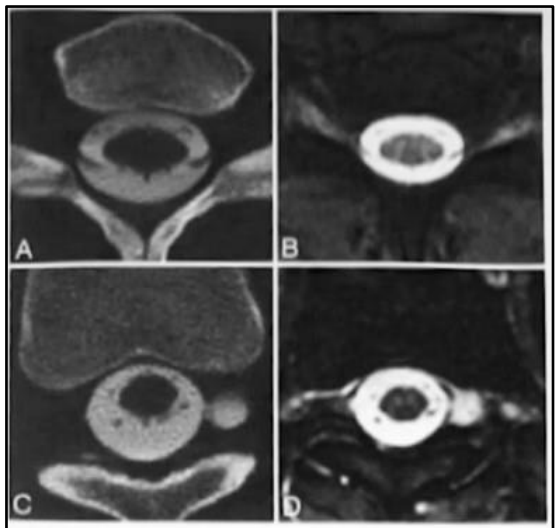

FIG. 2. CEMRM results for Case 5 in Table 1, a 22-year-old woman who presented with disabling orthostatic headache, nausea, and vomiting. A: A previous axial CT myelogram of the lower cervical spine shows no evidence of a CSF leak. B: Axial fat-saturation T1-weighted MR image at the same level as shown in A after intrathecal infusion of preservative-free normal saline shows MultiHance contrast agent extending outside the nerve root sleeves. C: Axial CT myelogram at the level of T-11 shows a nerve root sleeve cyst. D: Axial fat-saturation T1-weighted MR image at the same level as shown in C shows MultiHance contrast agent that extends lateral to the nerve root sleeve cyst.

Figure 8

If the leak can be localized with imaging, it can be targeted in this way either in the lumbar, thoracic, or cervical regions. There is not much reported in the literature about cervical blood patches, but they have been used and they have been successful. Of course, many neuroradiologists are quite concerned about giving any amount of blood clot or fibrin in the cervical region. The volumes provided there are about 10 to 15 cc's. The final method of treatment is surgery, but this is an option only if the CSF leak is well-localized.

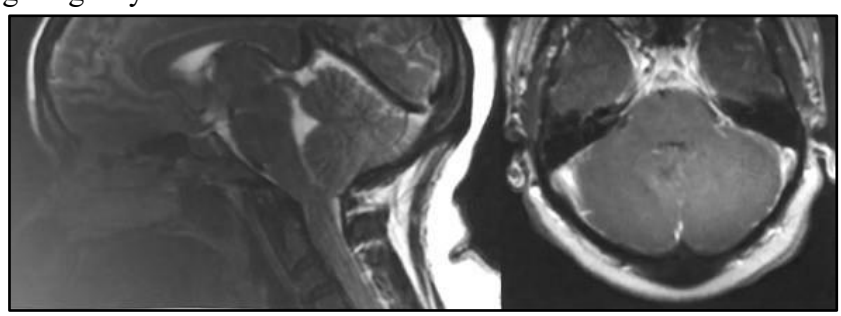

Figure 9a

This is a case from Dr. Gray (**Fig 9a**). This patient was seen by neurology in the ER with headache, weakness on the left side of face, slurring of words, difficulty closing the left eye, difficulty chewing due to left-sided weakness—obviously, the ER doctors were concerned with stroke. It was found, however, that she had MRI findings (**Fig 9b**) somewhat consistent

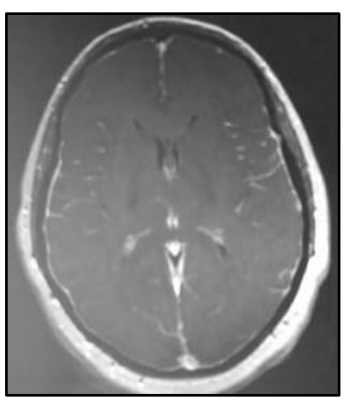

Figure 9b

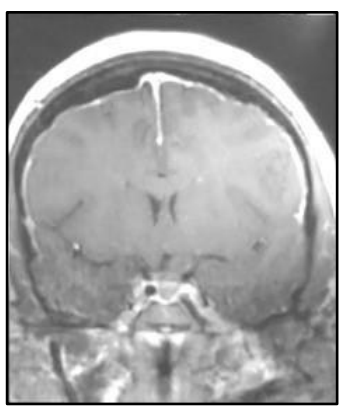

Figure 9c

with a CSF leak, including when they did enhanced study, enhancement of the dura. In this image (**Fig 9c**), you can see a very small fluid hygroma on the right side.

This is the CT myelogram done by Dr. Gray (**Fig 10**). These are dynamic studies performed while she has the patient on the table. You can see where she saw some fluid in the epidural space. One thing of note about this fluid is that it very often does not localize where the leak is actually located. So we may be tempted to do a blood patch where the fluid is, assuming that is where the leak originates, but it is important to remember that fluid localization and leak location often do not correspond at all, unfortunately.

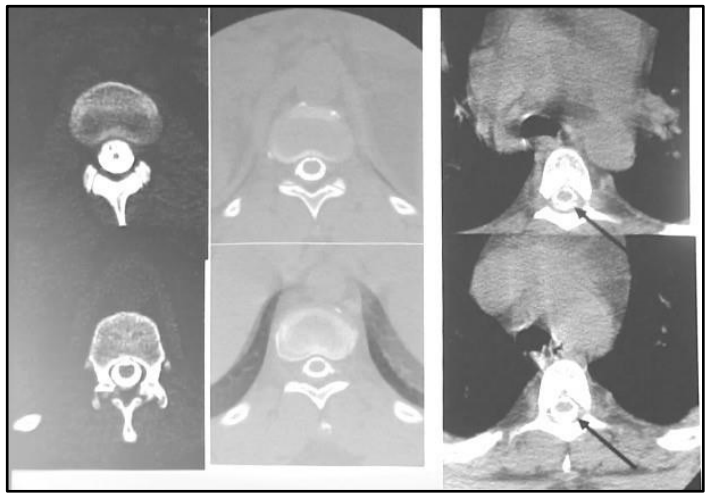

Figure 10

These are images of the sagittal views and the coronal view. The fluid that is collecting can be seen in the sagittal views **(Fig 11a)**, dorsal to the spinal cord. In the image on the right (**Fig 11b**), you are able to see the CSF leak much lower down on just the one side. Quickly, the leak was identified and actually right there on the CT table, it was targeted. Fibrin glue mixed with blood is injected right at the site where the leak is seen. The patient did well after this was corrected. What is remarkable in a case like this, then, is that the tiny little leak that was so hard to find proved to be extremely significant to the overall hydrodynamics of the whole patient.

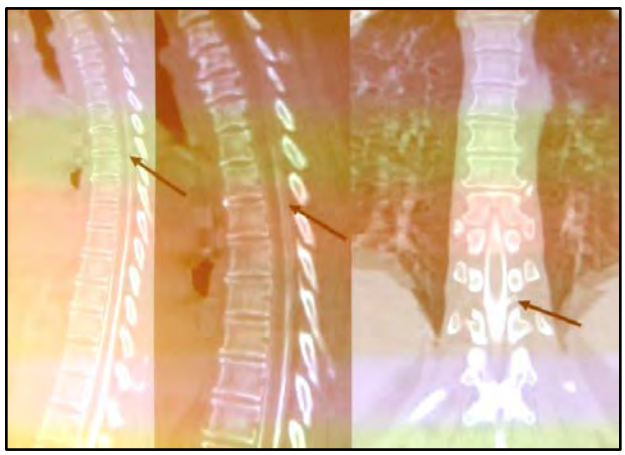

Figure 11a

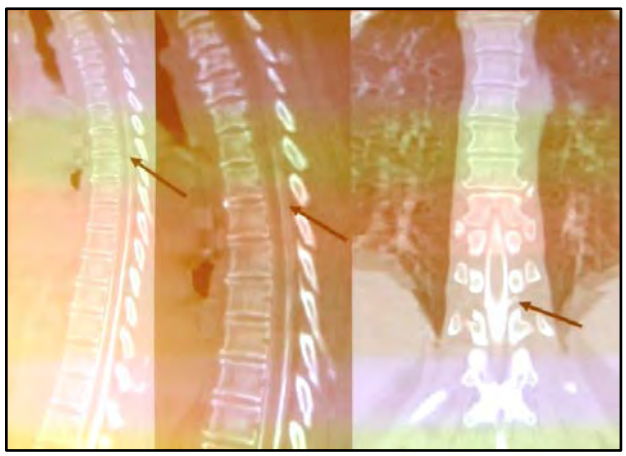

Figure 11b

In review, there are a handful of issues that we know. Headaches related to CSF leak or spontaneous intracranial hypotension are not so rare. The clinical symptoms of CSF leak are variable, and some of those

symptoms may overlap with symptoms commonly screened for in patients suspected to have Chiari. Images can miss the diagnosis and fail to identify the leak, even using fairly extensive, complete studies. When the leak is successfully found and treated by general or specialized studies, that treatment seems to be effective, which means that although some of these leaks are small and difficult to find, they are clearly significant.

There are many things, however, that we still do not know. For instance, although we know that some CSF leaks are difficult to find and that some headaches present with unknown etiologies, we do not know what proportion of patients that we evaluate have some occult CSF leak. I do not mean to suggest that all patients with similar symptomatology have a small occult CSF leak, but if even three or five percent of the patients we evaluate have CSF leak out of all the number of patients that have headaches or the millions of people that have Chiari malformations found incidentally by MRI, that small proportion would still be a meaningful amount of patients for our consideration.

We also do not know whether or not occult CSF leak and hypotension contribute to the anatomy and symptoms of Chiari. It is clear that hypotension does, in fact, contribute to Chiari issues when we are able to identify it— but could something similar be happening, even in the subtler cases of CSF leak? Could CSF leaks even help us to differentiate the symptomatic from the non-symptomatic patients who have similar anatomy? We may see similar amounts of compression and tonsillar descent in two distinct patients— one who has symptoms and another who is asymptomatic— and there are a lot of reasons that may occur, but I mean to suggest that one of those reasons may be CSF leak.

Another question to be answered: could the link between connective tissue disorders and Chiari malformation be a CSF leak, and not necessarily the hypermobility itself or some combination thereof? Often when I think about connective tissue hypermobility, I think of hypermobility at the cervicomedullary junction and related issues; but could it also be that there is a higher risk of CSF leak in these patients and that the leak might then be complicating symptoms?

Is it possible that CSF leak helps to explain why patients with pre-existing asymptomatic Chiari may develop symptoms after trauma?

Additionally, we know pseudotumor can also result in CSF leaks— so does this also explain a potential connection with pseudotumor?

And finally, and perhaps most importantly, could the failure of Chiari decompression surgery be resultant from a failure to recognize an underlying CSF leak? I think we all have to admit this is possible. The question then becomes how often does it happen and how can we better detect it after a surgical failure?

It is exactly the kind of case that we do not want to see: a patient who underwent a large decompression who has symptoms that never went away or that may have worsened after the decompression; the patient's opening pressure was zero was later found to have a CSF leak. We have to make sure we screen for these patients properly before we offer them surgery. I know we all think about this, but I think it is something that requires more careful attention.

One hypothesis that we had put together follow a general progression of: crowding of the cervicomedullary junction, hyperdynamics at the cervicomedullary junctionan, and anatomical progression or symptom progression over time as the tonsils continue to deform the cerebellum in the brainstem. We can add to this, then, that CSF leak, known

or unknown, may be contributing to this hypothesis at the second level, creating additional hyperdynamic changes, causing more sagging, and, of course, causing more deformation and symptoms. Also important to consider: trauma can cause a CSF leak and connective tissue disorders may facilitate any traumatic injury.

This diagram (**Fig 12**) helps to illustrate this complicated issue— but CSF leak may certainly play a role in this flowchart, even if we are not certain of the process in all cases. Of course, connective tissue disorders have other effects in ways not indicated on this diagram, and there are also aspects of inflammation that we are not discussing here. However, CSF leaks may play a role and connect many of the dots in the pathophysiology.

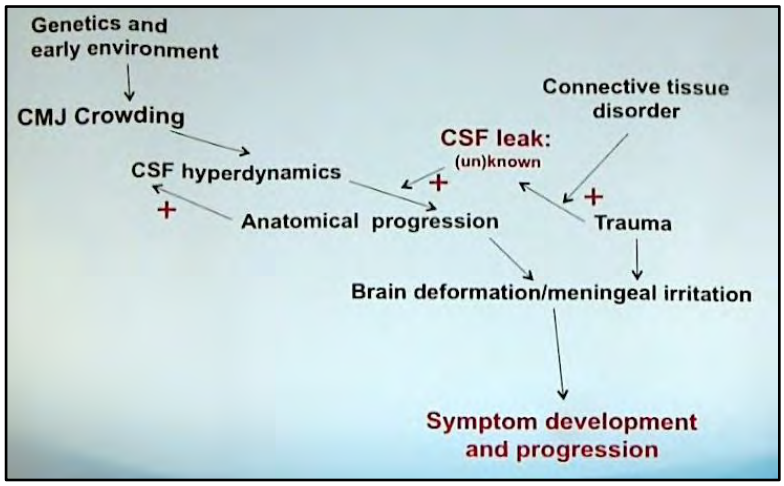

Figure 12

I came across one paper that, although not related to Chiari malformation, I found otherwise interesting because it reminded me of where we are in terms of Chiari and the sagging of the brain. This paper looked at subdural hematomas but in younger people, which is unusual because we are, unfortunately, more accustomed to seeing geriatric patients with subdural hematomas after a fall. This paper[7] looked at whether or not CSF leak and hypotension contributed to enlarged hygroma or subdurals in younger people. One paragraph in their paper basically said that they did not think this particular issue had ever been investigated. The authors acknowledge that it occurs with spinal taps and shunts, but question whether it could it happen in those who have spontaneous fluid leaks and occult leaks that were otherwise unknown.

They did a prospective study. Participants who had a chronic subdural were put through a particular protocol, involving the head and the spinal cord, intrathecal gadolinium injections, dynamic myelography – all the things that we have been talking about – to really explore the possibility of a CSF leak. They found that 25 percent of the patients – seven of the 27 – did have what were found to be proven CSF leaks. Again, this was not in patients with crowding of the posterior fossa, but subdurals. However, it is notable because the CSF leaks were not seen and were not suspected, unless they were looked for explicitly.

Another paper[8] that I only saw in abstract form a few days ago in Canada at a meeting, was a study conducted in patients with Chiari by Laurence Watkins in Queen Square, London. He used ICP monitoring in patients with Chiari malformation. And we all know that there have been recent findings of increased pulsatility and changes between the cranium and the spinal canal and things that reinforce this— so we know, then, about changes in ICP and pulsatility changes. He explored that in this small number of patients but found abnormalities in 14 out of 16 of them; and they led to Chiari

decompressions in only three of them. In others, he did shunting. There were three in which he found evidence from the ICP monitoring of low ICP, hypotension, who did better after patching. It is a small study, so we cannot do any substantial statistics on this but, again, when you actively look for this, you seem to be likely to find it.

What does all this mean for the future? We can investigate the involvement of occult CSF leaks in Chiari malformation by, first, doing what we are, hopefully, doing right now by increasing our awareness of the variable symptomatology that can occur with hypotension. Also, perhaps we can look more rigorously at those images ensuring we have a head MRI to look for hygromas, brain sagging, all those signs in any patient that we evaluate with Chiari I malformation. And, if we find any suspicion, either symptoms or imaging, we will then progress to more extensive testing using an algorithm for testing designed to find these leaks. Ultimately, I hope we can develop a method of looking for hypotension, noninvasively.

Obviously in hydrocephalus, we are trying this a great deal so that we do not have to stick needles in the spine in a situation where the patient already has a Chiari malformation— that is not an optimal diagnostic situation. So think in the future, we have to use the symptoms that present to us and the images we can take utilizing more extensive imaging techniques to find out how many CSF leaks we may have otherwise missed.

And just to reiterate one last time to continue to remind us all: an observed incidence of any phenomenon will be extremely low if you are not actively looking for it. So that is the purpose of this talk: to encourage us all to be more rigorous in our search for CSF leaks. Thank you.

Discussion following presentation

DR. HENDERSON: One comment: I did have a patient just a week ago, a 25-year-old with a large, chronic subdural hematoma, and no explanation. So I think that this might be a good explanation for that in an otherwise healthy young man.

And one question: Dr. Long and I have seen a fair number of patients with Tarlov cysts over the last 20 years and many of them, perhaps a majority, have a connective tissue disorder. But probably because I was not necessarily looking for it, I do not recall seeing any CSF leaks in that population.

DR. MARK LUCIANO: So again it may be difficult to find if you do not do the kinds of provocative imaging, and imaging with pressure. If you do a CT scan, sometimes you find leaks that are fast or slow. So it may be that there are CSF leaks that we just didn't find.

DR. HAROLD REKATE: That was an excellent review, Mark. I think we have different referral patterns, to some extent; but essentially all the Tarlov cysts I note, seem to come from CSF leaks. If you do the MR myelogram, that high T2 image, it lights up like a Christmas tree; there are Tarlov cysts at every level, from the midthoracic level, down. And I call it whack-a-mole because you fix one of them, and it may show up at a different space over and over and over again. It really is not that benign.

I, unfortunately, saw a patient who eventually died of continuing recurrent Chiari malformations from these brutal CSF leaks; and every attempt to stop it failed very

quickly. A fellow at Cedars-Sinai had a case report of that, too. So I would mention that it is not always completely benign.

DR. LUCANO: No. We have had patients who are comatose as well. It can be a very, very severe case.

DR. PAOLO BOLOGNESE: I am sorry my plane was late. I enjoyed what I could catch. From my experience with a case that I had both with Dr. Kula and with Dr. Milhorat in the past, we have encountered quite a number of these. I often wonder how many we missed as well.

All of them were somehow different from the standard Chiari malformation patient. In the beginning, we had a back-and-forth referral pattern; we were shipping from Cedars-Sinai at first, then we kind of developed our own little thing. It is not that difficult once you start dealing with it over and over.

But I do agree with you, it is grossly underestimated. We probably will not know the real number for quite a while.

DR. LUCIANO: I wonder if we should develop or agree upon some element of screening in all our patients with Chiari? I do not mean any type of invasive screening, but perhaps a list of screening items that can definitely be checked as part of Chiari I malformation evaluation, because I believe many people out there are not doing that.

DR. REKATE: What do you think about trying to encourage people to get an enhanced scan?

DR. LUCIANO: Yes— except I have been disappointed, when looking at the literature, with the sensitivity of the enhanced scan. And a lot of people rely a lot on that. This paper showed it to be very low; but other papers have shown something close to 60, 50 percent; it may not be good enough, especially in cases where it may not be that dramatic or high-volume leak.

I think, in many of those patients with that slower leak, which nevertheless, is hydrodynamically and clinically significant, the leak does not show up on those scans.

DR. REKATE: In my experience, every time I have been sent an intracranial hypotension patient without dural enhancement, I have done ICP monitoring; and the patients have all had either normal ICPs or high ICPs.

Now, it may well be that the high ICP patients have had their Tarlov cysts sealed before they get to me and they no longer leak at that moment. But it helps. It is such an easy thing to do, and I do think it helps.

DR. LUCIANO: I am glad you brought it up. I did not really mention ICP monitoring. ICP monitoring is something that we do quite often, too, if we are suspicious of this and cannot find the leak.

Sometimes the pressure looks entirely normal; and then, as part of our protocol, we sit them down and then we stand them up for 20 minutes. And I have been, I guess, surprised to see that it is only revealed in that fashion. And if you do not do that— if you

do not look for that positionality really well— you can also miss a low-pressure leak. Again it is small and may only affect a person when they are standing up for a period of time.

So you have to do that in the test. And we may be missing some slow leaks.

DR. TODD BELL: If I can broadcast my ignorance: has anybody looked at optic nerve sheaths, diameter ultrasounds as a serial marker or a way to screen for connective tissue problems?

DR. LUCIANO: I do not know that they have. My understanding of the optic nerve sheath is that the sensitivity of it, the diameter increases above 20 centimeters of water. I am not sure how, if it gives any information about a normal or low pressure.

DR. REKATE: Why would it show low pressure?

DR. BELL: Well, I am just playing around in my clinic. I actually have bedside ultrasound that I do optic nerve sheaths just for the additional information.

And what I have seen is that most of the kids that I treat that have either Chiari or joint hypermobility and dysautonomia symptoms typically have a widened optic nerve sheath, which would be appreciated if you would see an increase in ICP. And then the question is: if you have a spontaneous CSF leak, can you then compare and see a decrease to where the optic nerve sheath actually normalizes in width?

DR. REKATE: But not to diagnose low pressure?

DR. BELL: Well, as, I guess, a reflection of a lower pressure than usual.

DR. LUCIANO: Roger?

DR. ROGER KULA: (To Dr. Bell) How does that compare with optical coherence tomography (OCT) measurements and looking at the optic cupping and the elevation of the optic nerve?

DR. BELL: I don't actually know. I wish I had an answer.

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10. Mast Cell Activation Syndrome

DR. ANNE MAITLAND, MD

I can't tell you how much it is a pleasure to be here. I believe we're at the forefront of redefining many conditions that have come under our care. This cross talk and cross-fertilization of ideas, I truly believe we'll be able to help our patients, and also just advance the knowledge of cross talk of the immune system and the connective tissue disorders.

I would like to start with a story about my favorite four legged friends. While trolling the internet about stories about connective tissue disorders, I came across this gentleman's blog, Doctor J. John Symes, DVM, a veterinarian. He entitles the chat, "the key to collagen disorders" is Ehlers-Danlos Syndrome.[1] He pondered: "Have you wondered why dogs generally rupture cruciate ligaments during a certain time of their lives, about the same time that other dogs are blowing discs, developing heart murmurs, and suffering from immune-mediated diseases and that first big wave of cancer? Haven't you seen patterns that beg answers, like the same old breeds having this happen and even the same time of year?"

And that part of the year might be the allergic component. So people talk about allergic arthritis. This might be again a seasonal pattern of how the mast cells might be engaged using the Ig receptor. So the veterinarian goes on to say: "Why do they rupture those in one leg; and then six months or a year, sometimes to the day, they blow the other? That's the pattern we see in almost all immune-mediated diseases of tissue, whether it be the eyes, neurological system, or the kidneys. And what breeds of dogs are involved? It's the dogs that are the most food-allergic, isn't it? Labs, cockers, poodles, rotties, and labs again, English bulldogs" –

A side note, my older brother had an English bulldog, who ruptured two cruciate ligaments, in the spring after turning 2 years old, and she then had two mast cell tumors; here the human world and veterinary world intersect. Back to Dr. Symes. "How about the ones that does it the earliest in their lives? I have had English bulldogs and labs do it before two years. And how did we create these chondrodysplastic breeds of dogs anyway? Anybody seeing the newest anomaly, the munchkin cat?"

Evidence and conversations about the crosstalk between the allergic inflammation and connective tissue is scant, but I would like to some thoughts and reports about the prevalence of immune hypersensitivity disorders and mast cell activation syndrome in patients with connective tissues disorders, including Ehlers-Danlos syndrome.

Let me start with a brief comment about the difference between mast cell activation versus mast cell activation disorder. From mollusks to elephants, mast cells are hard-wired to act as the first line of defense after the surface area is compromised – skin, gut, respiratory tract. In addition to defense, MCs also have been shown to participate in homeostatic mechanisms as well.[2]

In the late 1970s, early '80s we started seeing an epidemic of immune-mediated, hypersensitivity disorders, from asthma to autoimmune arthritides.[3] The hypersensitivity epidemic seemed to rise out of the decline of infectious diseases, such as Tuberculosis, hepatitis and water-borne diseases as well. These early observations lent to the hygiene

hypothesis, which essentially implies that industrialized societies' success with vaccinations and public works for safe water and food supplies, may have opened the door to our immune system, no longer pre-occupied with infectious agents, now turns its surveillance and armaments on harmless substances, whether it is allergens, such as foodstuffs or dust or self-proteins, such as nuclear antigen or thyroglobulin.

For thousands of years, the immune system of our ancestors have been hardwired to fight off usual suspects for thousands of years, which pathogens and dangers have been for the most part eliminated. (**Fig 1**)

Like a soldier who's been at war for 25 years, who returns home, and does not know to stand down; the soldier ends up being a lot twitchier when they encountering very innocent objects; sounds, some smells, a fuzzy image triggers a danger signal; and the battle weary soldier basically revs up his defenses.

This is, in essence, the definition of an allergy-, where some innocent substance- a foodstuff, airborne perfume, or a cream provokes the release of chemicals from readily excitable mast cells, which may release these chemicals in a piecemeal fashion or through wholesale, across-the board degranulation. (**Fig 2**)

Once diagnosed with Mast Cell Activation Disorder, know that there are two different ways these soldiers securing our borders may go awry. First, a subset of soldiers commit mutiny on their own. In regards to MC biology, a single MC sustained a mutation in a key receptor, c-kit gene.

So essentially there are two flavors of mast cell ac-

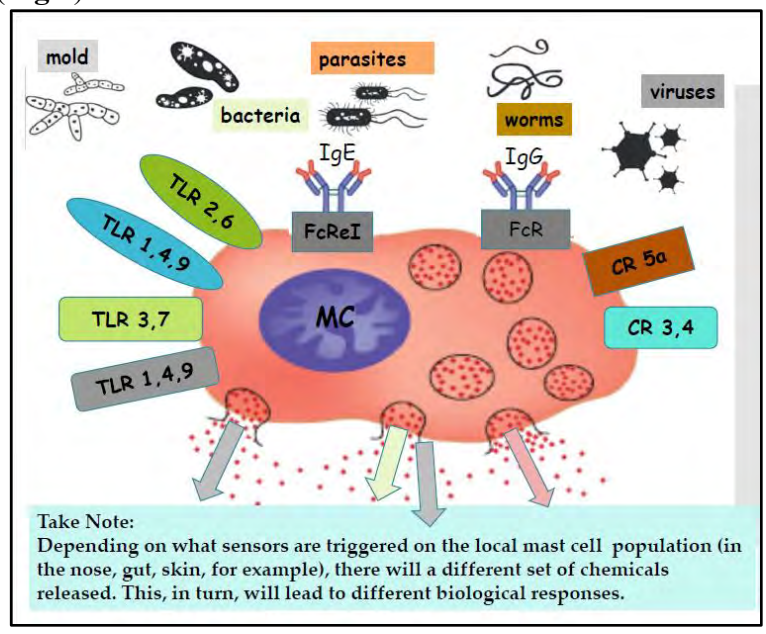

Figure 1

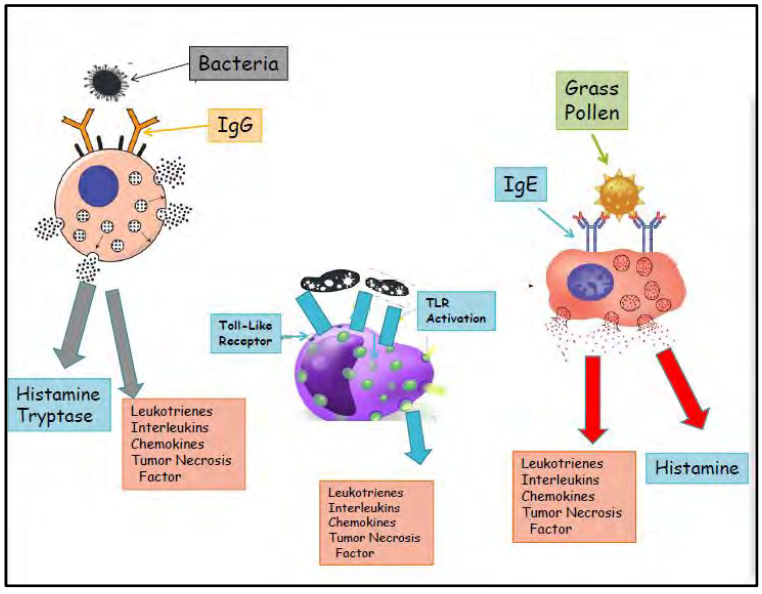

Figure 2

tivation disorder. this mutation lends a growth advantage to the affected MC clone, leading to colonies of rogue Mast cells. This is a rare condition called mastocytosis, and there are 200,000 estimated cases, world-wide. And then you have mastocytosis "junior" where these individuals actually do have a mutation in the c-Kit gene, but the phenotype is not as severe. And that's called monoclonal mast cell activation disorder, no different from what we see in the cystic fibrosis population, where different mutations in the CFTR gene are sustained. Depending on which part of the c-kit gene underwent a mutational change, the affected individual may have a more or less severe phenotype. This depends on the location of the mutation and a what stage of life did that MC clone sustain the C-kit mutation

The more common form of MCAD is the "non-clonal", non-proliferative phenotype, of which most allergists see every day: Rather than a few, rogue mast cells that are defying orders, most mast cells are that are being good soldiers, but the mast cells are following bad orders. That is, dysregulation of the mast cell compartment is secondary to another system gone awry. For example, if a child or adult has the propensity to make IGE to peanuts rather than a parasite, such as strongyloides or fish tapeworm, every time the peanut IGE sensitized individual encounters peanut, depending on the site of the encounter, will have an allergic reaction, from localized itch in the oropharynx (called oral allergy syndrome), to generalized hives (anaphylaxis, grade 1), to complete cardiovascular compromise (anaphylaxis grade- call 911 now).

Mast cells are over-reacting; they are not standing down after encountering a perceived danger. And this danger could be from without, an infectious insult, a toxin; or from within, meaning tissue damage, because mast cells will also participate in the cleanup/healing process, which for instance, might be what we see in women with their menses.[4] So we don't know necessarily, is it the estrogen/progesterone? Because mast cells do have estrogen receptors. Or is it damage from the endometrium turning over that then tells the mast cells to stand up and start participating as well?

The diagnosis of mast cell activation syndrome – is an evolving concept. So it was first coined in 2011. Please know that the consensus diagnosis for mastocytosis only came around in 2007; so mast cell activation syndrome really a very new phenomenon, even in the allergy/immunology world.[5]

I use a rule of three observations. And I was taught by several wonderful mentors. First. Are they showing signs and symptoms of mast cells misbehaving in, at least, two organ systems, if not more? Hives and irritable bowel symptoms? Asthma and flushing? Second, and this next point is a little bit controversial, depending on which specialist you're talking to. Many allergy/immunology specialists are accustomed to use of medications to determine a diagnosis response to medication. However, many patients with symptoms are prescribed newer generations of medications, but often say they felt better with Benadryl. Third, is there any evidence of overactive mast cells?

Too many providers rely on the tryptase as a marker. However, tryptase isn't always released during mast cell activation. Too often allergy/immunology colleagues, questioning whether or not the patient in front of them has a mast cell activation disorder, say, "Well, the tryptase is normal." But if you ask, "When do you ever see tryptase released during food-induced anaphylaxis?" Never. By focusing on just tryptase, little respect is being paid to a cell that contains chymase, heparin, tumor necrosis factor, platelet activating factor, and 40 other chemical mediators.[6]

Besides being used as a marker for mast cell activation disorder, tryptase has a job to do. Interestingly, Dr. Joshua Milner, at NIH, recently identified several families with "high normal tryptase levels" after one family member had been evaluated for mast cells activation disorder. Those found to have high normal levels of tryptase (between 9-20 pg/mcl) were deemed to have a familiar cause of mast cell activation, and had joint hyper-extensibility.

For Mast Cells, some dangers or situations do not call for tryptase to be released. So, it is recommended to look for other markers of mast cell activation. This includes the release of histamine, but take note that there are other repositories for histamine besides mast cells. Providers should also look for prostaglandin metabolites. Lastly, if blood and urine studies are not helping and one is still suspicious of mast cell activation disorder, check the tissue of an affected organ system.

So going back to histology, which is not done at the bedside or office anymore, tissue is the issue. The pathologist should use either anti-CD117 or anti-tryptase to identify Mast cells in the biopsied material. Otherwise, mast cells will not be seen under the light microscope. Unfortunately, the staining techniques that first identified these mast cells back in the 1800s fell to the wayside. But now some older stains are used to try to identify mast cells. Understand that mast cells were first identified under a microscope using stains that were used to dye clothes for the fashion of the day. When more sophisticated techniques were developed, mast cells were no longer sought.

H&E stain won't pick it up. The reason why the mast cells are able to pick up those stains is depending on whether there are acidic components in the granules or basic components, they'll latch onto different types of dyes at the time. So they'll either light up blue or purple depending on which one you use.

It is important to rule out other disorders that may be contributing to the similar phenotypes.

So all the time, people come in and they say, "I'm allergic."

And I'm like, "Great. What does that mean? What part of your body is affected, and what's doing it to you?"

It is important to understand, that depending on where the mast cells are misbehaving, you can have any organ system involved. So mast cells are commonly residing in the parts of the body that are chronically exposed to the environment; the skin, the gut, and the respiratory tract. However, they can be recruited to any hot spots, because that's their job. Some patients have IBS-like symptoms. A Brigham gastroenterologist identified in his patients with IBS – and most of the patients were women – that most had monoclonal mast cell activation disorder as well. Gastrointestinal distress is not uncommon. However, mast cells are not that specific. Engaging more than one receptor may result in a much more profound effect, with more rapid degranulation and recruitment of other mast cells.

So to understand how a person develops a certain allergic phenotype with mast cell activation disorder, it is important to understand how these mast cells are educated by the environment they inhabit.

The mast cells are born in the bone marrow. An analogy would be a candidate who joins the police academy, gets basic training, and then is sent to different communities, where the "rookie" police academy graduates must learn how to serve that particular community. They have to learn how to respond to that environment. So if somebody is

walking around “off-kilter”, that would not be such a trigger for the police officer on 42nd Street and Broadway; but in Scarsdale, NY, it's a huge warning sign.

Given climate change, changes in our food and water supplies, the over-use of antibiotics, storage materials other than glass, tin and paper, our environments have been altered dramatically in the past 30 years. Our hard-wired mast cells, designed to recognize usual suspect dangers, that were removed from our day-to-day experiences less than a generation ago, have become confused and dysregulated, overactive when the situation has no evident danger; or, alternatively, underactive, with an inability to respond to true, possibly new dangers. Most people have a tendency to focus on foods, which are easier to control, but remember that our bodies have to respond to changes in temperature too. Cells will behave differently in culture. Temperature can change the activity of the cells. So, in addition to foods one must consider the impact of temperature, as well as chemical exposures, that are exposed to our skin, our gut, and our respiratory tract, which in turn, may inappropriately recruit the mast cell population to go to DEFCON 3.

There are two major receptors responsible for the differentiation of mast cells in the tissue and the activation. The c-Kit gene, responsible for homeostasis of the mast cells in the local environment, and separate genes for activation of the mast cells. The mug shot to recognize parasites is IgE.

Allergists tend to use the term "allergies," as opposed to "IgE-mediated mast cell activation disorder. For diagnosis they use allergy skin tests, or ImmunoCAP. Regarding ImmunoCAP, there's a problematic 20 percent false-negative rate.

For activation, mast cells employ a plethora of chemicals depending on the danger to which they are exposed including histamine, heparin, platelet activating factor, tumor necrosis factor, interleukin-3, interleukin-6 and also respond to several factors in the environment. Depending upon the environment, there may be flushing, hives, itch, or swelling; gastrointestinal nausea and genitourinary discomfort, vomiting, abdominal and uterine cramping, and urgency. A bad peanut allergy may manifest as gastrointestinal distress or allergic rhinitis. Depending upon the season, a peanut allergy may vary; for instance, a peanut allergy may be worse in the springtime, because a bad tree pollen allergy appears to have a synergistic effect upon the peanut allergy.

Regarding cardiovascular issues, there is a relationship between postural orthostatic tachycardia syndrome (POTS) and allergies. For instance, a 14-year-old patient diagnosed with narcolepsy had the same breakfast every morning – almond Cheerios; it became evident that she was allergic to almonds. Changing her diet, resulted in resolution of the POTS, and the narcolepsy went away.

Regarding neuropsychiatric problems. Data suggests that of the phenotypes of adults and children with mastocytosis, the first two complaints with which they present relate to skin or gut. Dr. Hamilton at Brigham who reported on IBS, showed that these women with IBS had mast cell activation disorder, and noted a third set of complaints that were neuropsychiatric in nature: mood disorders, sleep disorders, headaches, behavioral changes. It was universal across all of these studies as well.

So allergic problems translate into this compromised or impaired executive function – memory loss, change in behaviors, sleeping patterns – that are all affected by this interaction of mast cells engaging in the environment and releasing factors that might directly affect how the nervous system works, or how the cardiovascular system alters delivery of metabolites to and away from the brain and the peripheral nervous system.

The figure gives a 3D effect of what is going on in the local environment. Mast cells have many granules - they're chock-full of preformed mediators: histamine, tryptase, kinase, carboxypeptidase, heparin, platelet-activating factor. Within minutes, the production of prostaglandin mediators and interleukins begins, and depending on what the mast cell will see, they will call in other mediators to "help". (**Fig 3a, 3b**)

Using the analogy of the police officer, if a police officer sees a fire, he will call the fire department; if he sees a person down, he'll call the ambulance; if he sees a bank being robbed; he'll call in the SWAT team. Similarly, if mast cells see a parasite, they will call in the eosinophils. If they see a bacterial infection, they will call in neutrophils; if they see a viral infection, they may call in lymphocytes. And they'll also change the local environment, because the connective tissue has the ability to upregulate and downregulate certain type of defenses, which are peptides that also have the ability of having antimicrobial activity as well.

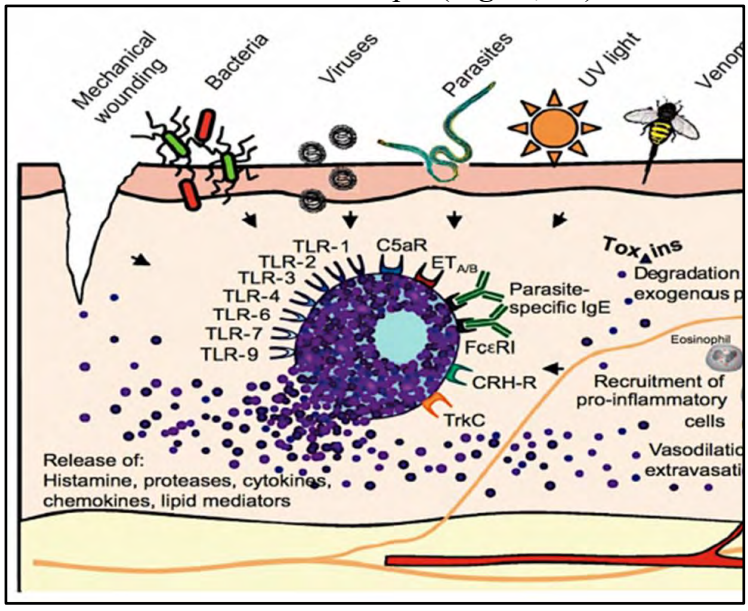

Figure 3a

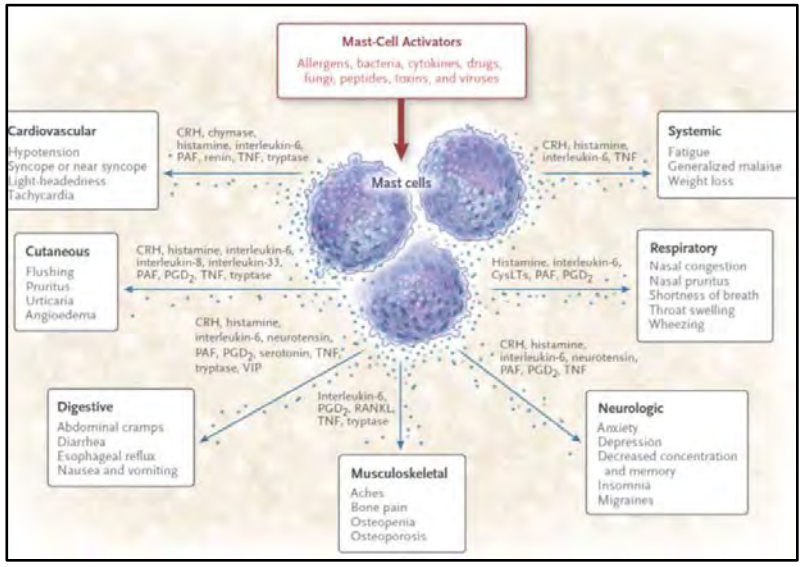

Figure 3b

As regards homeostasis, mast cells have the ability to respond to physical stimuli. People can get hives from vibration, solar energy, or cholinergic stimulation. A young lady who made the Daily News last year because every time she played on the soccer field, she ended up with laryngeal edema

And facial edema, such that she had to quit the sport that she loved. This person did not respond to histamine blockade, leukotriene blockade, or prednisone. The only molecule that worked for her was omalizumab (Xolair). So there are different ways of kind of

quieting the mast cells down, different interventions in order to help these individuals get their mast cells a little bit more quiet and under control.

In addition to physical stimuli, there are certain cytokines, especially stem cell factor, which helps to increase the presence of mast cells locally. Interleukin-33, amplifies degranulation of mast cells; and this is derived from connective tissue. There are also neuropeptides, including CRH, and substance P causing pain and itch factor.

There are direct or indirect communications between the mast cells and the peripheral and central nervous system: so adhesion molecules, depending how they're engaged, might cause secretion -- and this is a two-way evolution. So the nervous system might be secreting to the mast cell, or the mast cell might reciprocally engage the nerve molecule.

When it comes to histamine, there's a reason why Benadryl was found in NyQuil. Benadryl can cross the blood-brain barrier and cause sedation. However, ten percent of patients who get Benadryl will become agitated. Parents who need to travel, and give Benadryl to their children, may do a trial run, and may find out that the child is doing cartwheels in the aisle because the Benadryl is actually agitating, as opposed to sedating.

Depending upon how mast cells degranulate, there is cross communication. A Hopkins study of patients that died from asthma, showed mast cells will migrate closer to the cells with which they're cross-talking. So they'll move closer to the vasculature, or to the nerve fibers; so there is a movement from a secreting situation to direct, cell-cell contact.

It is important to understand that there are a lot of receptors on mast cells besides the IgE receptors. Toll receptors, a receptor for adenosine phosphate, cytokine receptors, complement receptors.

Some patients with Ehlers-Danlos Syndrome (EDS) have mannose-binding lectin deficiency, rendering them at increased risk for infection. These patients may have a harder time dealing with the biome that's sitting on the surface area.[7]

For example, here is a pathogen that's engaging a surface toll receptor. This cell will release lots of factors, including leukotrienes, interleukin-1, and tumor necrosis factor – causing a fever with – interleukin-6, GM-CSF, and chemokine CXCL8. There will not necessarily be histamine or tryptase; there are many different parameters besides just tryptase.

Here's a cell that's engaging an anaphylatoxin with a C3A. In this case there is the release of tryptase – a protease that will allow modification of the local environment, as well as histamine, in addition to leukotrienes, interleukin-6, tumor necrosis factor, and these other chemokines just mentioned.

Engagement of the Fc receptor can be IgG aggregates, causing a serum sickness type of activity. When it comes to evaluating patients, with suspected mast cell activation disorders, it is important to look for other comorbid disorders- the bad orders that the "good" mast cells are receiving.

For instance, in a patient has common variable immune deficiency the average time to diagnose this after onset of symptoms for primary immunodeficiency is up to 12 and a half years. Similar to many other immune-mediated disorders.

People can suffer in an immune dysregulation setting with not having enough cells, complement, or antibodies, and not know it. Typically, when it comes to immune deficiency or immune dysregulation, patients may present with recurrent infections, severe infections, and other autoimmune phenomena. This phenomenon gives insight as to how

patients can present with hypersensitivity reactions. Some of the data has been borrowed from individuals that have mastocytosis, and monoclonal mast cell activation disorder.

Dr. Escribano from Spain, has a large number of patients that have been diagnosed with Mastocytosis[8], the work of Escribano and his colleagues serves as an important resource for the recognition, diagnosis and management of mastocytosis. In this case series, the most commonly reported symptoms were of the skin, gut, and then neuropsychiatric issues. Only a quarter of with mastocytosis present with anaphylaxis. Respiratory symptoms might significant, but health care providers consider rhinitis a nuisance rather than a clue, and patients typically are not screened for rhinitis and asthma.

As a side note, our diagnosis and management for those affected by asthma is poor. Less than 15 percent of primary care facilities have spirometry or a screening questionnaire to see whether or not they have a patient that has reactive airway disease. We wait for somebody to have a serious attack to say, "Okay, you have an asthmatic condition." And this is very important when you're trying to identify someone that has mast cell activation disorder, since one needs at least, two organ systems that are impacted by mast cell dysregulation. So respiratory tract, skin, and gut and neuropsychiatric issues are all very common.

In the (non-proliferative /non-clonal) mast cell activation disorders, there is the study at Brigham and Women's adult IBS clinic, where the investigators identified 20 patients with symptoms beyond the GI tract; and

Dr. Hamilton and colleagues started asking, "Are you having problems in other organ systems?" in addition to the abdominal pain, which is probably why GI was the number one presenting symptom, compared to the Escribano study on Mastocytosis, skin and neuropsychiatric manifestations and symptoms were most common.[9]

So there's something about either the factors that the mast cells are elucidating or the impact that they have either on the vasculature, the connective tissue, and the central and peripheral nervous system that may be impacting into again sleep disorders, mood disorders, POTS-like phenomena as well.

Diagnosis has often featured serum tryptase. But the diagnosis for mast cell activation disorder does not rest upon whether the patient has an elevated tryptase.

For instance, one patient and her husband had a lovely dinner on the Upper East Side. They both had co-morbid poisoning (seafood poisoning from excessive histamine that develops in certain decaying fish).

The husband was well after two days, but the patient continued to have hives and angioedema for one year. It transpired that she had mast cell activation disorder, but her tryptase baseline was always five. Once under control, the patient's baseline tryptase was two. It is therefore important to recognize that if the baseline tryptase is below the normal, and increase of 20 percent may be diagnostic for mast cell activation disorder. So, it is important to know the baseline tryptase level in any patient with mast cell activation disorder.

Another important level is the prostaglandin- the eicosanoid metabolites; so getting a 24-hour urine histamine, prostaglandin D2 or an F beta PGF2 alpha have been extremely helpful for diagnosing mast cell activation disorder in individuals that have a connective tissue disorder.

Histology should not only stain for a CD117, high affinity receptor for IgE, and activation markers. The presence of a CD117-, CD25-, or CD2-positive cell, mast cell, lends to the diagnosis of mast cell activation disorder.

Patients can identify a single event that caused them to be unwell. One woman had anaphylaxis to a shot. Another motor vehicle accident, and others toxic exposure at work. Patients in general have symptoms that were worrisome for their mast cells abnormality, but then some event accelerated the symptoms.

For treatment, the anti-IgE molecule is omalizumab, the Xolair.

But many patients stumbled onto Benadryl, and felt better. And there are three generations of histamine blockers. The first generation worked better; but unfortunately, has a tendency to mostly cause sedation, and some percentage will actually have agitation.

Doxepin, amitriptyline, and nortriptyline are helpful.

Allergists/immunologists use it for hives, angioedema.

Gastroenterologists use it for IBS. Neurologists use it for migraines. Again that common theme: skin, gut, respiratory tract, neuropsychiatric issues.

Corticosteroids work well in many of these patients; but doubling up on the concentration of steroids may cause other issues. Patients start to complain about neuropathic issues.

Cromones are now available for the nose, the gut, the respiratory tract, and great for the skin as well.

Leukotriene blockade. There are three leukotriene modifiers:

Singulair, an oral leukotriene receptor antagonist is the least effective; Accolate, is more effective, but requires a function test; and Silo or Zileuton, which works on the level of the production, and is more effective than the leukotriene-receptor antagonists.

Finally, a Japanese study found that in a group of children with diagnosis of urticaria pigmentosa or cutaneous mastocytosis, that many had 816 mutations, although many had mutations outside of the 816.

So if you're really suspicious of a patient having mast cell activation disorder and you have the resources, it might be worthwhile to go ahead and screen the gene. The best tissue is bone marrow, unless what you have there is an infected organ.

Typically, some other organ system has to be involved to warrant subjecting somebody to a bone marrow. So going from mast cell activation to mast cell activation disorder, this is a resting mast cell under electron microscopy. This is one that's undergone degranulation. (**Fig 4**)

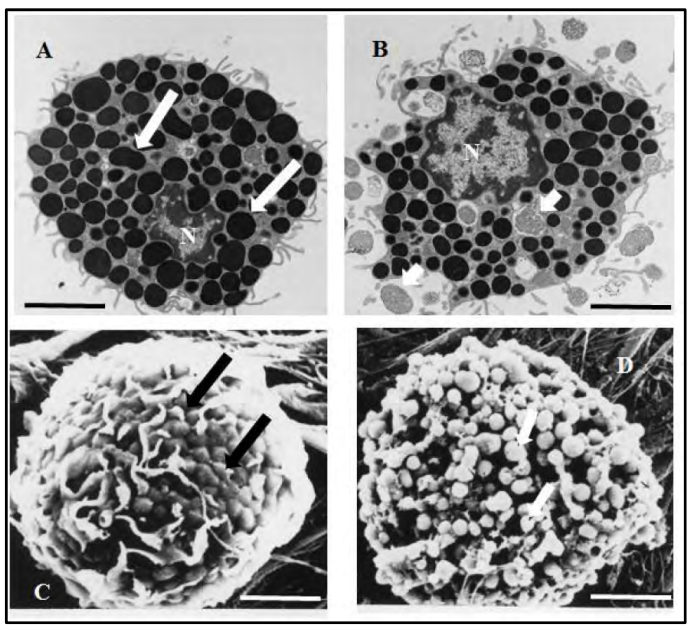

Figure 4

These are the common complaints that people come through

the clinic: hives and asthma with the change of season; facial flushing and gastrointestinal distress; ragweed causes gastrointestinal distress; actually have anaphylaxis to fresh fruits and vegetables, in addition to having skin symptoms. So again skin, gut, respiratory tract.

There may be a receptor, yet to be identified, that may be contributing to non-celiac but gluten sensitivity as well.

When it comes to other syndromes that can contribute to mast cell activation disorder-like symptoms, it is important to consider cardiac conditions, endocrine conditions, and occasionally screen for carcinoid; one woman with hyper adrenergic mast cell activation syndrome, instead dropping her blood pressure, became hypertensive at 160 over 110, and tachycardia, with heart rate to 100.

Immune dysregulation can also mimic mast cell activation disorders and should be ruled out in neurologic and psychiatric conditions.

Various skin conditions -- angioedema, atopic dermatitis, chronic urticaria – may be isolated, without having mast cell activation disorders. Mast cells are participating, but are not the driving force.

It is now apparent that there is cross talk between the nervous system, the vasculature, and the immune system, specifically the innate immune system. This may be manifest in POTS and neuropsychiatric conditions. Peter Vadas, an allergist/immunologist in Canada, found that POTS, EDS and mast cell activation disorder co-aggregate, which has prompted others to state that "If you can't connect the issues, think connective tissue." (10)

The problem with some of the lab testing is that it focuses mostly on the adaptive immune compartment. Mast cells are part of the innate immune compartment; and they have other ways of being activated, other than antibodies.

To know what's going on with mast cells requires looking directly at the mast cells themselves.

There are two different versions of mast cells. On the one hand are mast cells that have acquired a mutation primarily in the c-Kit gene, and on the other mast cells that are “just following orders”, and it's just a question of what kind of orders are they getting. Most allergists are familiar with this as having IgE made not to a parasite, but rather to pollen, cats, antibiotics, chemotherapeutic agents. This is very common. I just saw a family of three. POTS, connective tissue disorder. This boy has already had his cervical and thoracic spine fused by the time he was 17 years of age. It turned out, he has selective antibody deficiency. And his sister has common variable immunodeficiency. Thus it is important to do a baseline screen of serum immunoglobulins and also get a lymphocyte subset. T cells and mast cells directly talk; in another case study of four patients with idiopathic CD4 lymphopenia, these patients were CD4-lymphopenic, they had lost the regulation of the mast cells, which were overactive.

A 65-year-old gentleman, ended up in Delirium Tremens because he liked having his toddy every night, but he could not tolerate hard liquor, and changed to wine; he started having problems with red wine, so he changed to white wine. But gastrointestinal distress and malaise from the wine prompted him to stop. He went into withdrawal, and could only be calmed by Valium.

It turned out that he had Kounis syndrome (vasospastic angina due inflammatory mediators following an allergic insult) in his 30s, suffered a right bundle-branch block

with a reaction, and underwent cardiac catheterization. He also had non-IgE-mediated anaphylaxis to stinging insects, and was on allergy shots for 20 years. It was found that the patient had transient eosinophilia; his doctors couldn't understand why his eosinophils would go up and then go down repeatedly. It was because his mast cells were calling the eosinophils out. Measuring the serum tryptase was not helpful. He was evaluated for carcinoid. He was found to have more than 40 mast cells per high-power field on endoscopy. (15 is the top end of normal).

Then the patient started having tremors, peripheral neuropathy issues, asthma exacerbations and then food pollen syndrome with anaphylaxis. This illustrates that the immune system will keep on pressing forward until the registered "danger stimulus" is gone, and it will start recruiting in help from the adaptive immune compartment.

When it comes to the diagnosis of mast cell activation disorder, do you have somebody who is having episodic symptoms come and go, whether it's the skin, the gut, the respiratory tract; mood disorders? So women who have peri-menstrual symptoms, are of concern.

The terminology out there is histamine intolerance. But this term neglects the fact that mast cells have many chemicals besides histamine. DAO supplement helps break down histamine, but the results have been uncertain. The leaky gut, histamine connection is still poorly understood.

Unfortunately, there are only six places in the U.S. taking care of patients that have suspected mast cell activation disorder: Brigham and Women's - Cem Akin and Mariana Castells (although their preference is to take care of patients with mastocytosis); Josh Milner at NIH, and he is interested in families with multiple affected people with high tryptases.

Here's where most of the patients are: They may or may not have an elevated or sustained tryptase, elevated histamine, or prostaglandins. It is more probable to see some abnormalities in the tissue themselves; so it's worthwhile to biopsy the skin, the gut, the respiratory tract or, perhaps, in some cases the tethered cord.

Discussion following presentation

UNKNOWN: Montelukast can cause suicidal behavior. So you said there were two other drugs that you might use?

DR. MAITLAND: Yes. If they have suicidal ideation or nightmares with Montelukast, more than likely, it will happen to Zafirlukast, as well as Zileuton; so that's off the table as a treatment modality.

Consider using the tricyclics agents might be helpful for some of those patients as well.

UNKNOWN: Again that's wonderful, Anne. How did these cells get so damn smart? I mean they're the evilest creatures on earth, it sounds like.

DR. MAITLAND: You know; I guess we've been arguing in the allergy/ immunology community for a very long time. Mast cells are found in, like, frogs, worms -- they're everywhere.

I think we have just so dramatically changed our environment. One of the things that have been argued is the discontinued use of aspirin. So aspirin is an interesting story, in that, it has been used for thousands of years, and it was used up to about the late 1970s, according to my pharmacy and pharmacology friends. And it was pulled off the market because of Reye's syndrome. It made a comeback when they found that it was helpful for preventing heart disease and stroke. And now they're starting to show that it's helpful for the prevention of certain cancers as well.

We use aspirin for our patients that have mast cell activation disorder. It's actually a very effective agent if they tolerate it. And even if they don't tolerate, you can always desensitize them to it; but that's something that needs to be done in a unit in order to do so.

We've also changed our living environment. The example I use is I grew up in the Bronx. If it was cold and Thanksgiving, you put on a sweater, you didn't turn up the heat to 72. The foods that we eat are no longer locally raised.

So I would just say, this mast cell that's used to a certain type of microenvironment is just completely confused and now completely overactive.

UNKNOWN: Thank you, Anne. That was very educational. So if we were to do some correlation with some clinical testing in order to, say, to support that the mast cells also do something in the tethered cord syndrome, would it be that urine test that you mentioned because that was the most specific and sensitive test?

DR. MAITLAND: That's been the most sensitive in patients so far that have a connective tissue disorder, unless they have another comorbid immune-mediated disorder.

So some simple things are questionnaires. Do these patients have symptoms that are worrisome for allergies otherwise? So there are standardized MIDAS questionnaires, asthma questionnaires, which will also lend to the diagnosis that mast cells are misbehaving in more than one organ system.

I mean the focus here is the nervous system. And then when it comes to looking at factors, I would stain – not only would I look for the numbers of mast cells that are there, but what are they doing?

Do they have activation markers that are upregulated? So that's where the CD2 and CD25 comes in. And another one that's been implicated is CD30.

And then also my guess is they have symptoms elsewhere. I have a little boy that has mastocytomas all over him; and he has respiratory issues, gastrointestinal issues.

And the nose is a wonderful place to biopsy because it's readily accessible, you don't have to take them into the OR to do that, and then to go ahead and stain.

You can also do nasal prostaglandin metabolites. I mean, there's lots of different ways. I'm working with Dr. Li -- and that's one thing I did not bring up. I'm actually working with Xiu-Min Li, who is a full professor at Mount Sinai at the Jaffe Food Allergy Institute. She actually uses traditional Chinese herbal therapy, along with acupuncture and acupressure, which has been very effective for a lot of these patients. It's a slow road, but it definitely is very helpful. She's published peer-reviewed literature.

UNKNOWN: Could you say a few words about the notion that acupuncture works, suggests that the sensory component of the autonomic nervous system is implicated in this?

DR. MAILTAND: I had a patient who suffered a traumatic incident. She went from being an executive for a Fortune 100 company to going to the emergency department every other week. She could not tolerate any medications, was hyper-adrenergic, so that her heart rate would increase to 150; so I couldn't give her epinephrine. I gave her a dose of Zyrtec that was compounded, and she reacted to it. And I was scared to give her Benadryl.

So Dr. Li actually taught me two moves. And before my eyes her pulse and her blood pressure came under control. I'm like, "That can't be." So I let it go. The heart rate went back up again. Pressed it again, and the heart rate came down again. I'm like, "Okay. I still don't believe it." So you only start to do it three times, right? So I let her go again. She went back up again. And then finally, okay, she's feeling better when I was holding -- my office manager held one side, and I held the other.

Dr. Li has identified four points that have been very important for keeping the autonomic system under control, with the notion that the mast cells migrating closer and allowing much more intercellular communication with the autonomic nervous system.

And also we're using other things too. To get the connective tissue under better control, we're using vitamin C, Quercetin, and other elements that are known to kind of have the connective tissue behave a little bit better. We're using Epsom salt baths and contrast showers. And patients are getting better. It's slow and steady, but it seems to be effective.

UNKNOWN: Does vitamin D have any relation in here? It's thought that it's effective in all cells and it may regulate T-cell function, and whatnot. We hear about it in MS and everything. What's the story in mast cells and vitamin D?

DR. MAITLAND: That's like the 800-pound gorilla in the room. Up to this point it's been shown to affect regulation on the R and A level regarding producing certain type of markers up to this point. But it's varying because it's such a heterogeneic group where you have a lot of individuals that are vitamin D deficient, their gut's not working, so they're not absorbing very well. We have a tendency to be very aggressive at trying get the vitamin D back up into normal levels, and that seems to be helpful up to this point.

But they still haven't done a strong correlation, that I've seen, trying to explain the mechanism of that.

UNKNOWN: Anne, what about chelated magnesium?

DR. MAITLAND: You know, I've had, not only the chelated, the -- here's the MTHFR gene story also.

I have some patients who do very well with it, but I also have some patients who have increased distress with it as well. It's a processing issue definitely on the level that we know. It's not only with methylation.

We are starting to appreciate that you have endotypes where you're having changing of how RNA is being processed and also how DNA is being kind of remodeled, depend-

ing on the chronic phenotype that's now happening in this new environment for the patients. I have a tendency to start off with not necessarily, you know, magnesium glycinate. I usually go with gluconate or oxide if they can tolerate it, or citrate.

A lot of them can't tolerate how it's processed because sometimes you can have trace elements in there THAT will kick them off. So that's why I kind of tend to stick with the magnesium citrate that's found in Calm, and just have them titrate up slowly. And that's also with the Epsom salts, you have the magnesium delivery as well; so instead of using the gut, you're using going through the skin. That seems to be well tolerated.

We're using probiotics. And they have to be very sensitive about which probiotics they use as well.

And then everyone is on a restricted diet. The histamine-free diet kind of goes against all that's known regarding foods -- not all but a good part of it that goes to foods that we know that directly activate mast cells.

So we recommend no nuts, no soy, no egg, no milk, no wheat -- it's easier to tell people what they can eat, as opposed to what they can't eat. I'm happy to give you the list, I have a copy of it with me. I'll send it out as well.

But I usually have them try that diet for only two weeks because I don't want them getting nutritionally compromised, especially somebody who's having the POTS, the mast cell going on, and then also the issue with their chronic turnover, their connective tissue.

UNKNOWN: What about proton pump inhibitors? Any part of this story? There's a question as to whether they interfere with B12 calcium and vitamin D absorption. More than 50 percent of our patients are all on proton pump inhibitors.

DR. MAITLAND: The nice thing about famotidine, cimetidine, and ranitidine, is they're H2 blockers. And then the tricyclics work on H1, H2, and H3. And you're less likely to have the interference with absorption of those elements if you go that way.

The thing about the proton pump inhibitors, they only work for 16 hours; so they're going to need something at night if they're taking it in the morning. And then they end up having to get B12 supplements, and also they have to do sublimable vitamin D in order to get it in.

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11. Pain of Musculo-Ligamentous Origin in Chiari

DR. JOHN MITAKIDES, DDS, DAACP

Thank you. I am basically going to talk about the pathophysiology of headaches in the hypermobility population. I will most closely be talking about the temporomandibular joint and upper cervical stability and how they work back and forth. I am a dentist by trade so, naturally, TMJ is sort of right in my wheelhouse.

The traditional thinking of temporomandibular joints was that the pain originated from a malfunctioning mandible in the structure. But in looking at the TMJ, hypermobility, Ehlers-Danlos syndrome (EDS) and Chiari populations we found that there is a direct and distinct relationship between the cervicocranial position and the TMJ position.

Essentially, the mandibular positional aberration creates the deflection of the mandible and its associated musculature, which, in turn, causes a deflection of the superior pharyngeal constrictor. This, in turn, causes a deflection of the cervical spine, especially evident in C2.

The C2 vertebrae is going to be our mainstay in talking about stability here. Whenever I examine a patient, C2 is one of the structures that I examine. Last time we were talking, Dr. Henderson and I were discussion how I can actually palpate the structures. To me, this actually seems to be one of the mainstays for diagnosing this condition.

We are also going to talk about a particular syndrome later on— and keep in mind that when we came up with these ideas and perceptions, we examined 200 diagnosed Ehlers-Danlos patients, 195 of which had a cervical instability problem. Thus, we have started to form the preliminary conclusion that if we are seeing an EDS patient, we are likely seeing a patient with a cervical problem.

In talking about TMJ headaches, the classic TMJ headache is a classic tension headache; they are caused by stress, clenching, muscle spasms, ischemia and neurological input to the trigeminal nerve and the Circle of Willis.

The trigeminal nerve is one of the inputs that will cause a neuromuscular migraine. Osteoclastic compression, degeneration, inflammation of the TM joint structures and meniscal displacement – all of these can cause they call "TMJ-type" headaches. That is your tension headache. Now, it is important to keep in mind that there are a series of muscles and these muscles are what actually generate the headaches themselves.

An EDS patient, initially, is hypermobile; in other words, they can open their mouths 75 millimeters. What that means is that they can put their fist in their mouth and a variety of other silly tricks. They do these things all the time. But after a while, they will injure the joint to the point where they can only open 20 millimeters, the width of one finger.

The large muscle on the side of the skull is called the temporalis muscle. When the muscle is tender at the anterior portion, the bite is towards the rear of the teeth. If tender at the center portion, the person is clenching straight down. Finally, if the rear of this muscle is tender, the jaw is retruded. When you touch the side of the head as someone does these different things with his or her jaw, you can actually feel the fasciculations of the muscle and you can track where that pain is going to present and what might cause it.

There are other muscles of interest. The masseter is another muscle that will give you discomfort. The rest of them, although they are very pertinent, will not give you a true "headache" type of pain. There are also muscles in the anterior triangles of the neck and the occipital triangles: the anterior belly of digastric, the omohyoid, superior pharyngeal constrictor, and the middle pharyngeal constrictor. These last two are really going to become somewhat of a nemesis for us.

In talking about suspension, the temporomandibular joint actually has some cartilage in place. That cartilage is what allows the jaw to move; so when you open the jaw for the first 33 millimeters, you will actually feel the rotation. This rotation is non-stressed. When you open the mouth a little wider, the joint will actually track.

So, in looking at our patients, we like to test this by placing two fingers on the side of the face and have the patient open his or her mouth. You can actually feel the condyles track out and that is normal. If the condyles do not track, you have a problem.

The meniscus (the cartilage) acts as the spacing between the mandible and the skull itself. The temporalis muscle length and the masseter muscle length depend on the height of that cartilage. When it displaces, you end up with pain and you cannot open your mouth.

Now, there are a handful of structures that cause pain in that joint, which we will see here (**Fig 1**). The ones that cause the biggest problem are the anterior synovium and the posterior synovium. This is actually a two-synovial fluid joint, upper and lower: above the cartilage and below the cartilage. There is a temporomandibular joint ligament, a posterior laminate, and a number of other structures that will cause discomfort. But the anterior synovium and posterior synovium are the two major areas.

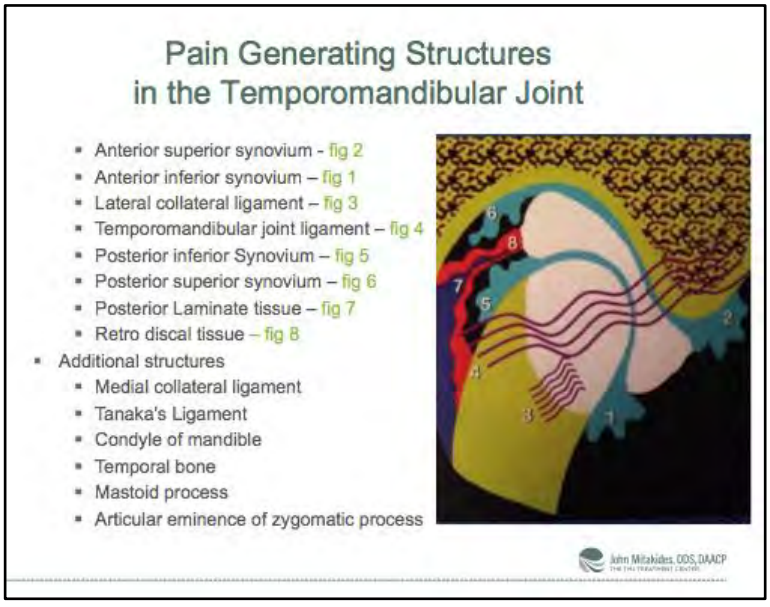

Figure 1

There are also three nerves that come in to this area posteriorly. So when this cartilage displaces, which we will see in a moment, the head of the condyle actually pushes against it and causes pain in the ear and in front of the ear.

There are a handful of things that can go wrong. For instance, if you open your mouth and it looks like this (**Fig 2**), that is not right—it means your jaw has dislocated to the one side. Some other issues include limited opening (a dysfunction), deviations which usually occur from the affected side, ligament or tendonous pain, joint sounds like jaw cracking or popping, and displacement of the condyles if the jaw dislocates.

This is a normal example (**Fig 3a**). The cartilage sits between the condyle of the jaw and the skull. The joint forms somewhat of a ten to four o'clock position; so when you open your mouth, the jaw tracks forward on the cartilage (**Fig 3b**). When it is dislocated, the cartilage comes forward. If that happens, the head of the condyle actually moves forward into the posterior ligament tissue. What happens perceptively when you look at the jaw, you will see the jaw rotated up because of the lack of support from the cartilage.

Figure 2

There are some other relevant muscles in the neck that I just want to mention quickly include the internal oblique muscles, rectus capitus minor muscles, trapezius muscles, semispinalis capitus muscles and the levator scapulae muscles, which will become very prominent in a minute.

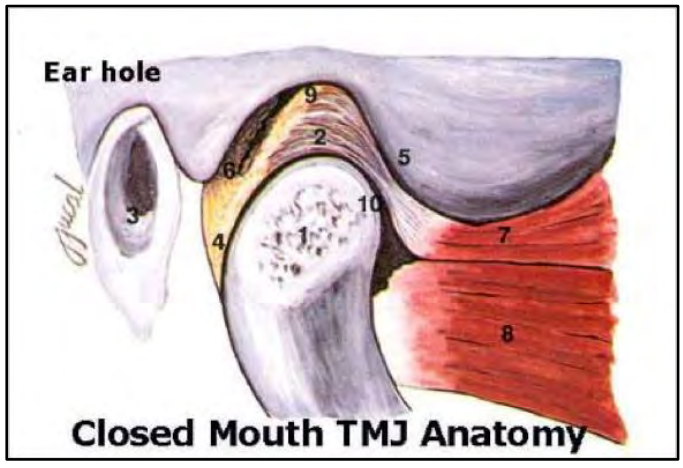

Figure 3a

We all know the neurology of the system; but one thing we should note is that we do have a branch of C2 from the trigeminal nerve going to the neck. Keep in mind that V1, V2 are all sensory; V3 goes anterior belly of digastric. There is the lateral rectus muscle of the eye—when there is input from the trigeminal nerve, sometimes you will get blurring of vision from the lateral rectus so I may ask my patients about blurry vision.

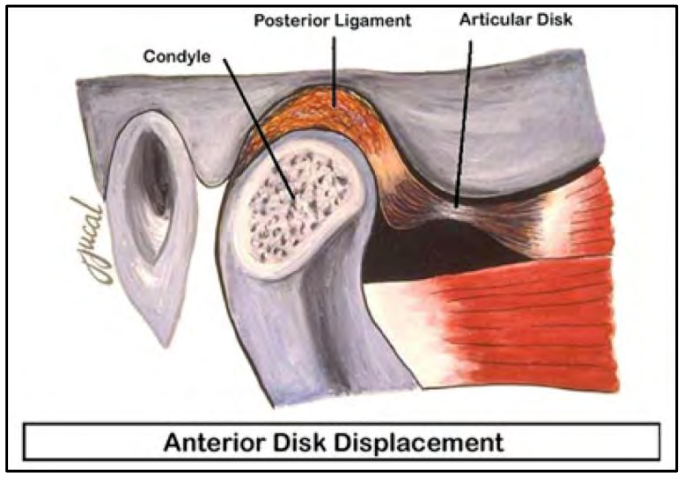

Figure 3b

Next we are going to discuss TMJ, oropharyngeal musculature but, specifically, cervical positioning. What happens is this: there is a muscle called the mentalis muscle, which is located in front of the chin. It is attached to the orbicularis oris, which is then attached to the buccinator. That buccinator muscle is attached to the superior pharyngeal constrictor in your throat. If you squeeze your teeth together and you feel a little void right in your cheek, you are noting the end of the buccinator. That is where the superior pharyngeal constrictor starts; it then extends all the way around the back of your throat, attaching to the other side.

The superior pharyngeal constrictor comes to the posterior wall of the throat and to the opposite side so that when you swallow, that constrictor actually closes down; and that is what puts the material or fluids down your throat. That serves to stabilize the rear of the throat.

But guess what is in the rear of the throat: vagus nerve, accessory nerve, hypoglossal nerve, sympathetic trunk, alar fascia, glossopharyngeal nerve, internal carotid artery and the facial nerve – they are all in front of the superior pharyngeal constrictor. When there is a distortion of that constrictor – if the throat is sore, if the patient has EDS and the tension in the throat is not what is should be, if there is a problem with REM sleep where the throat will go atonic at night – all these structures can potentially become distorted, especially the alar fascia, which extends from C2 to the skull. When there is displacement of C2, there will likely be a distortion of that posterior pharyngeal constrictor. The middle pharyngeal constrictor basically stabilizes C4, but most of the problems we will see will originate at C2.

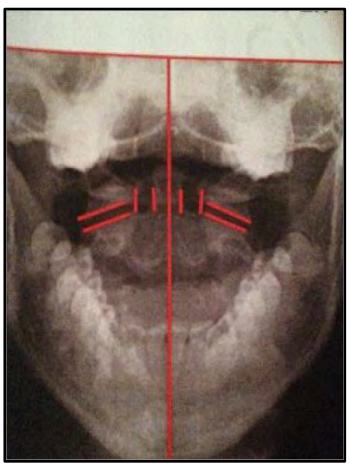

Figure 4a

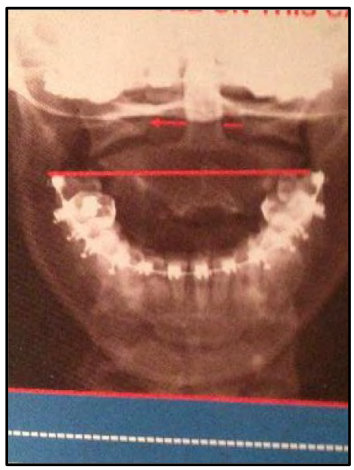

Figure 4b

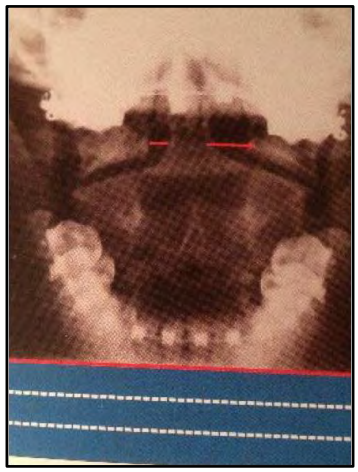

Figure 4c

Now, we are going to get into craniocervical instability and this will be the kicker right here. This is the dens in center position (**Fig 4a**). You can see that the spaces are equal, side-to-side; but if you look at the occlusal plane, it is level. Over here, the vertebra is actually rotated to the right (**Fig 4b**) — the space is increased; but look at the occlusal height: it is higher one side than the other. When rotated to the left (**Fig 4c**), we observe the same. The occlusal plane of the mandible actually deflects when the vertebrae deflect in the neck.

So, basically, if the jaw is out, the vertebrae may be out; if the vertebrae is out, the jaw may be out. If you are examining a patient, maybe you can look and see which way they open their mouth. If there is a deflection, chances are that there may be a deflection or rotation of C2.

This is what I show when I am giving presentations to a patient audience (**Fig 5**). On the left, they can clearly see the rear of the dens in a posterior view. I will also show an open mouth— if someone looks down an open mouth and down the throat, they can clearly see the anterior roots of C1. In this final image on the right, they will be able to see the rear of the dens and spinal cord and what it will actually compress against.

Something to note: C1 will rotate, most of the time, in the same direction that C2 rotates.

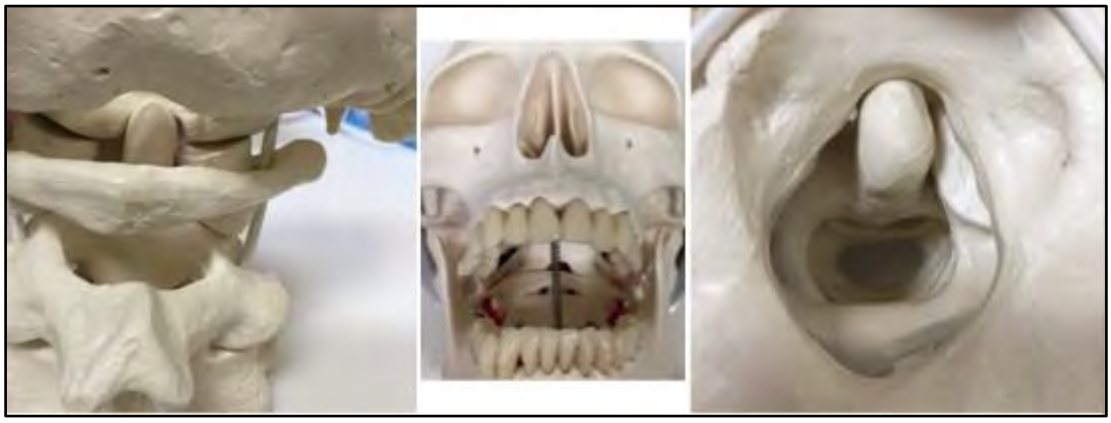

Figure 5

Next, I want to talk about the myofascial pain syndrome, which I have not heard anyone else describe as of yet. It is a referral pain syndrome related to cervical stability proximate structures, including Chiari, that are influenced by mandibular and cervical distortions. Basically, what happens is the mandibular positional change causes a superior pharyngeal constriction, and the muscle constriction then causes tension in the cervical plane, producing evulsion in C2. When the C2 evulses, the stabilizing musculature will cause the levator scapulae muscle on the opposite side of the rotation to go into spasm.

The levator scapulae muscle is the muscle that goes down your back and underneath your shoulder blade. That is the knife that you get under your shoulder blade when you are standing at the sink, doing the dishes; that is the tightness there. The levator actually attaches from C2 to C7, going down your back.

When C2 rotates, it will actually take the lateral tubercle of C1 with it. So, in other words, if you reach right behind your ear and feel some tenderness, that is the lateral process of C1 and it can show you the rotation of C1.

Usually, if you can feel both sides of the rotation of the vertebrae, that means C1 is rotated forward; if you get just one side of the other, it will tell you to what side C1 is rotated.

Another way to test this is how we do it in our clinic— test the head rotation. If head rotation is limited, usually the side that is limited in its rotation is the side to which C1 has rotated. If you cannot move your head from side-to-side in a tick-tock motion, that means that C2 is limited. For example, I can move my head in a tick-tock motion to the left, but not to the right. I crushed my neck playing football, so I have three vertebrae in my neck that are junk and this limited movement is the extent of my full rotation. For me, everything is compressed on the right-hand side, so I can only really go to the left. That is generally how we clinically test what is going on in which direction for these patients.

Also, the prominence of C1 behind the ear will actually cause compression of the sternocleidomastoid muscle. That is the muscle that will come down the side of your throat. The longus colli actually becomes tender as well, and that is the muscle next to

your trachea that we call the whiplash muscle. When that becomes tender, that means you have had a whiplash and/or you had a dislocation of the vertebrae.

C2 also causes compression of the greater and lesser occipital nerve. The greater occipital nerve extends up the back of the head and the lesser occipital nerve extends behind the ear. I have found over the years that when the greater occipital nerve has issues, the occipital muscle is affected. From there, there can be aponeurosis on the top of the skull and that is the pain the patient feels on the top of the head. From there, the issue extends to the frontalis muscle, translating into discomfort over the top of the eye and also putting compression on V1. Compression of V1 causes the pain that the patient experiences on the back of the eye.

Theoretically, aponeurosis involves displacement of C2 or the mandibular malposition. That will cause deflection of C2, causing the positional change, spasm in the levator, pain behind the ear, pain in the anterior neck and pain that is referred over the top of the head. What I have found, especially in EDS patients, the minute that I find that the dorsal process has rotated out, I will go through each of these issues with the patient and find clinical signs of each of these in that patient. It is, unfortunately, a very defined situation.

In conclusion, it is very evident that the mouth and the head are close integrated. We talked a little bit about how the trigeminal nerve input sometimes causes migraine. The input and mandibular position affect the muscle position, cervical torsion, and resultant aberration of associated structures.

Chiari and surgical procedure outcomes may be influenced by the mechanical and neurological inputs due to skull and vertebral positioning as a result of skull fixations and other alterations of the upper cervical spine.

What that means to me is that if, in fact, C2 is out and the jaw is out of position, that may affect the final outcome of your Chiari surgery involving fixation, especially if you are performing a fixation of C2. If, in fact, it is in the wrong position, you may actually have maintained pain behind the ear, anterior throat, rotation over the top and/or pain by the eye.

Now, I am not claiming this to be gospel, and I will not say that we have "corrected" but rather rotated the vertebrae back into place in the patients that we have seen or referred out in order to stabilize everything. This way, when you are able to do the surgery, you might get a better surgical outcome.

Essentially, what I mean to suggest to you is that the position of C2 may affect your Chiari decompressions. The velum at the back of the throat can be part of the dysautonomic that you have heard about due to the distortion. The pain in the anterior portion of the head and the side of the head can actually come from the same, but different sources—TMJ and the neck. If a patient comes in and I ask them to identify where their headache is localized and they point to their temples, I know to look for TMJ; if the patient says it is localized in the front, I know to look at the neck because it is likely referred pain.

I like to do things practically. I am the guy that sees three to five new TMJs per day. As far as EDS patients go, I probably see two to three hundred per year— relatively speaking, the clinic sees a lot of them, giving us a chance to actually evaluate. As I had mentioned earlier, we kept a careful track and of 200 EDS patients, 195 of them had some level of cervical instability. Dr. Henderson knows that I share patients with him

frequently. Dr. Bolognese and I have shared a patient before, as well. This overlap makes it easy to find the connection, but, at the same time, it is interesting to see.

At this point, I do want to mention that I only do this pre-surgically. If you would like me to see any patients before surgery, I would be happy to do so; but if you have already operated, then I really cannot do much for them.

Discussion following presentation

DR. FRASER HENDERSON: If you examine a patient and they open their mouth and the palate is tilted to the left, I suppose— I am not sure which one is tilted? Is that the side to which C1 and C2 are also rotated?

DR. JOHN MITAKIDES: Usually what happens is that when C2 goes out, it will actually torsion the musculature to the point where the jaw will pop to the rotated side and when the patient opens his or her mouth, you will hear some popping.

I have learned over time to develop a method to rotate C2 back in, as a diagnostic tool. When we rotate C2 back in, the head will turn fully again, the popping will go away, and the torsion of the jaw will go away, as well.

As far as the jaw deflecting to one side or another, it is a little confusing in the fact that if the vertebrae rotates to the right, the dorsal process will go to the left. And the dorsal process is what causes the spasm from the levator underneath the left scapulae, behind the left ear, and above the left eye. But the vertebra is actually rotated to the right, so the jaw will actually deflect to the let because of the deflection of the cartilage. So, keeping track of it, if the jaw rotates to the right, everything will present on the left; if it rotates to the left, everything will happen on the right. But you will actually see a rotation and/or a popping of the jaw, telling you that you have a physical displacement.

DR. HENDERSON: Thank you.

DR. ROGER KULA: How do you manipulate C2?

DR. MITAKIDES: There is a methodology. There is a fella, a good friend of mine, his name is Mariano Rocabado from Santiago, Chile. We worked out a way to use two muscles in the neck to put torsion on them and actually lift and rotate C2 in the neck.

DR. KULA: Can the patients do it themselves?

DR. MITAKIDES: I often show them how to do it, themselves— absolutely. We just finished doing this in London last week with Prof. Grahame.

DR. PAOLO BOLOGNESE: I actually saw a European physiatrist doing similar maneuvers.

We have seen very often in Chiari I malformation that the patients have micrognathia, overbite, and high palate. Also, for a while previously, we were seeing in older patients with Chiari that TMJ anatomy was just way more compressed than the usual,

more relaxed cases you have shown today. So all of these patients, invariably, were having TMJ problems.

DR. MITAKIDES: Right. Exactly. And basically, what you are going to find out is that when the neck rotates, the cartilage will displace.

DR. KULA: I have come in contact with a couple of osteopathic doctors that call themselves atlas orthogonists; they believe they can manipulate the atlas in certain circumstances.

I do not know what you feel about that, but I have seen a couple of people after a trauma who have this displacement of the odontoid to one side or the other. The radiologists who have looked at it thought it was kind of physiologic and it may not be anything real. It is almost like what you had showed earlier with the odontoid slipped to one side— they have a lot of neck pain. I do not know, but maybe there is something to all that.

DR. MITAKIDES: The thing that is interesting about that is that you can actually take someone that is rotated and rotate them back in afterwards; the dens was in the center and the patient can then rotate his or her head— the limitation was gone.

DR. PATRCIA MEEGAN: I was reading your handout earlier and it said that you refer your patients out to physical therapy.

Do you find that the physical therapists that you are referring out to actually know how to treat the TMJ with the Rocabado method and the intr- and extra-oral manipulations?

I am a physical therapist and actually for all my patients I use C1 and C2 self-corrections when they are having these issues. I even have them do the self-corrections post-surgically, even if they are not moving, because it seems to rebalance those musculatures.

But we are finding a lot of hyoid dysfunctions in there as well, with the hyoid rotating and then affecting the facets at C3, adding that into the whole complex.

DR. MITAKIDES: Playing with two cans of worms there.

DR. MEEGAN: Yes— that is why we tend to see them, because we know how to treat that. But I have found that we always get all the TMJ patients because the dentist says that they do not treat it other than by prescribing a guard.

DR. MITAKIDES: I train PTs on how to do the manipulation, number one.

Number two, I train those same PTs on how to read a face and body to determine on which side of the body the limitation is found. You can tell by positioning of the shoulders, the rotation of the head, the shape of the face, which side is weaker or stronger, et cetera.

You can actually read someone's face at a cocktail party and tell them which side is acting up and which is not. The running joke at my clinic is that I can look at some-

one and say, "Oh, tell me about that knot underneath your shoulder blade" and that person will be taken aback at how I know about it without his or her mentioning it.

I have taught very many PTs in and around Ohio the Rocabado technique, but I would caution about using it after surgery.

DR. KULA: I am just curious: usually we think about TMJ as its own separate issue, all by itself. But what I am gleaning from what you have said is that patient with EDS have the craniocervical instability, which begets the TMJ dysfunction—meaning the TMJ is a secondary problem to the instability, versus the way that I have been so used to thinking.

If the patient has a bad bite or someone has all their teeth removed and they have bruxism, that is a different kind of TMJ problem, is it not?

DR. MITAKIDES: Unfortunately, and I hate to say it, it is the way it should be treated. Because the classic example is a patient who receives a crown and no matter what, the patient just cannot get the bite correctly; this is because the problem is not originating from the position of the jaw, but it is originating from malposition of the vertebrae.

So when I actually go to check a patient's bite, I am going to make sure that the vertebrae are in position before I actually check the occlusion because otherwise I will have the patient grinding on their teeth the whole day looking for the wrong problem. It ends up being an "upper cervical problem," rather than an occlusion problem.

DR. KULA: I find that interesting. It is a different perspective than I had previously held. It is definitely something to think about.

DR. ULRICH BATZDORF: How far do you have to get the patient to open his or her mouth before you are able to determine whether the mandible is mal-aligned? Anyone can open it a little bit, presumably, without asymmetry.

DR. MITAKIDES: Normal opening is 40 to 55 millimeters. EDS patients can open it sometimes to 75 millimeters. They literally can fit a baseball in their mouths. They will do that four or five times and then all of a sudden, they will injure the joint and can only open 20 millimeters. That is pretty common.

But look at the deviation: you look at the way the jaw actually rolls, when you open your mouth and it moves to the right, that means you have got a subluxation to that side, nine times out of ten times.

But it is not unusual to hear popping on the opposite side because it is doing all the work and this one is sitting still.

12. Increased Intracranial Pressure

DR. SUNIL J. PATEL, MD

Thank you for giving me the opportunity to present today. When I was invited, I did not know how I would fit in with this expert crowd on the diseases that we are discussing. But I may have something to contribute; so hopefully, you all get something out of it. I know I have already gotten a lot out of this.

My topic title is Increased Intracranial Pressure, and just one hypothesis on how sinus outflow obstruction may be contributing to this disease. I'm a physics major from college and I really appreciated the first talk this morning. I really believe in more dynamic manners of looking at and diagnosing these diseases.

I do not have any financial interests to disclose.

We all know how this broad group of patients with increased intracranial pressure and other related conditions presents. They are very tough cases. They have headaches. They can be overweight females. In South Carolina, I probably see a lot more than elsewhere in the country. I believe our average BMI is probably ranked number one after Alabama. These patients come in with headaches, visual problems, tinnitus.

Most of us know that when these patients come to us as neurosurgeons, they have generally failed medical therapy. If you look at all the evidence, all the stuff that has been written about it, including our own experiences, we realize that there is very limited class III evidence that shunting, whether it is an LP or VP shunt, really works. There is a high rate of shunt failure.

These patients frequent our offices; among the eleven neurosurgeons in my department, none of them want to manage them, so they unload them onto me.

A few years ago, probably over a decade or so ago, folks started looking at the dural venous sinus drainage. There have been single-case reports wherein as many as a little over 50 patients report having dural venous sinus stenting done to treat intracranial hypertension.

Immediate results have always been good; but again, while they have been good and the endovascular folks are getting to be real experts at it with very low complication rates, the long-term durability of these stents to open up the sinus has not been well studied.

I just want to share with you what our experience was in a period of about five years with 118 patients whom we saw with refractory increased intracranial pressure. We found a sinus abnormality on MR venogram in 43 patients, and subjected all of them to venography.

We only found 43 that had an abnormality as well as a sinus pressure gradient of 8; we put in a stent. Technically, these patients did well. There were no complications. Immediate results were excellent; they had improvement in headaches, et cetera.

But the long-term results were not so good. Seventy percent of these patients continued to have improved headaches at an average of about 22 months follow-up, and only a little less than half had improvement in their visual fields and acuity after stenting. Two of them required re-stenting for thrombosis.

This is just an example (**Fig 1**) of someone who has a stenosis in their tranverse sinus. This shows how the stent is deployed.

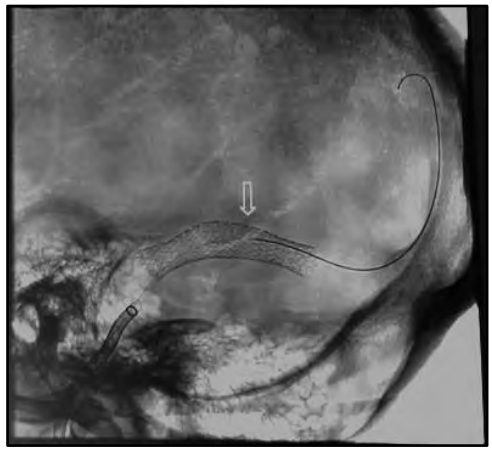

Figure 1

We have five endovascular surgeons. Most of the time, they are busy taking clots out of the head, doing thrombectomies; but sometimes they take care of these patients, as well.

Interestingly, about 92 percent of the stenotic lesions were in the transverse sinus. One patient had stenosis in the sagittal sinus and another had stenosis bilaterally with bilateral stents.

As I said, there were no complications: 100 percent technical success, just a tad over 75 percent long-term, six months for us. Average follow-up was 22 months with visual improvement.

So here again, class III evidence with no long-term positive results; and clearly, we are missing the boat. As physicians, when we are faced with something that we do not understand, we ask questions.

We really do not understand what psuedotumor is. We really do not understand what increased intracranial pressure is. Is it a CSF issue? Is it a more dynamic issue of venous hypertension? Is it a swollen brain? All of us know the brain just looks swollen, suggested by our first speaker who gave a very, very nice talk on water dynamics at the cellular level. Are these patients suffering at that level? Do estrogens have something to do with the aquaporin? What about the overwhelming prevalence of woman with this disorder? We just do not know.

So in looking back at all this, I could not help but notice some interesting things that we observed. When we were doing these conventional venograms, sometimes I diagnose the patient, and I am going to show you an example.

The picture on the right is prior to a lumbar puncture evacuation of CSF. (**Fig 2**) When we evacuated CSF and did a high volume of CSF drainage, the supposed stenosis in the transverse sinus disappeared.

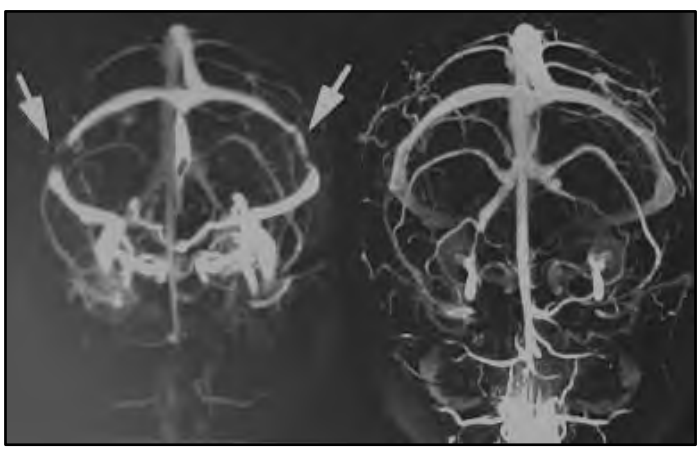

Figure 2

So this was an interesting question for me. I found myself asking: What came first? Did the raised intracranial pressure cause the stenosis? Or was the stenosis causing the ICP? Or, alternatively, is this some sort of dynamic process?

There's ample literature on either side. There are folks who propose that it is the stenosis that is causing the IIH and that is how we wound up with several reports of patients who are being stented.

Then, there is the other side to be considered. Are we just putting a stent in these patients when they perhaps just happen to have a lax sinus wall and some event causes increased intracranial pressure, compressing the sinus and resulting in this dynamic development of increased ICP?

After about two and a half years of convincing the IRB that I can put an external ventricular drain (EVD) in these patients and do provocative testing during the venography, we are now taking these patients with increased intracranial pressure, putting in an EVD and measuring their pressures for 24 or 48 hours and take them to the angio suite. When we do our routine conventional venography, we measure the gradients, and then we do provocation by infusing 5 cc's of preservative-free saline into their ventricle to raise ICP. We also do another test with the Valsalva and see what is happening to the gradient.

The study was just approved about a month ago, so we do not have results as of yet. We have completed testing on one patient; unfortunately, I could not get the ICP to increase with only 5 cc's. I'm a little bit stuck now—but there are more experts in the room who may have some advice on what to do in order to better understand what the sinus physiology has to do with this syndrome.

There is another interesting study on which we have embarked – which did not require much in terms of approval—is meant to study the pulsatility index, as has been established by neuroradiologists, on the sinus wall as it is seen on the MRI scan. This is being added to our pressure gradient study to try and find a noninvasive way of looking at the laxity of the sinus wall in these patients, and determine whether or not we can find a correlation.

We are also measuring the pulsatility index in patients with no IIH but some other pathology in their brain for which they are getting an MRI scan, to establish some normative data.

Right now our group is determining whether we should do a randomized study looking at either stenting of the sinus or diversion of CSF. We are still working out the kinks to see how we are going to approach the IRB for this type of study. For instance, when you have established the fact that there is a gradient, how are you then going to randomize between stenting and CSF diversion?

I do not have the same level of knowledge on as some of the individuals in the room so this was a shorter talk, but these are the research areas in which we are digging. I'm actually looking forward to some advice and comments on this area of research.

Discussion following presentation

DR. HAROLD REKATE: Nice talk. It certainly brings up a lot of interesting questions.

It was recognized very early that this was a positive feedback loop—that something triggered it, the pressure would go up, and then the vein would collapse and so forth. Brian Owler in Australia, I believe, showed fairly well that by interrupting the feedback loop, you can lower the pressure and treat the patient.

I limit this procedure to those pseudotumor patients who are thin— for those patients with BMIs over 40, not so much. That is really compelling for the Chiari and syringomyelia patients because your brain gets bigger if you have high venous pressures

in your right atrium. The brain actually swells up— we know that. We also know that bariatric surgery will be curative in this form of pseudotumor. So rather than putting them through stents, I would recommend that they have bariatric surgery.

I think it is wonderful that you can shunt the transverse sinus, I think that is great. I've got a patient who I would love to stent the sagittal sinus. But since the clotting off of the stent is relatively, though not tremendously, common, I worry about whether or not the patient would not survive while we are messing with the sagittal sinus.

So my question really is what led you to the courage to stent the sagittal sinus?

DR. SUNIL PATEL: I recognize the fact that, you know, it is a serious problem if you thrombose the sinus.

First of all, we have not seen it in the 43 patients that we have done. So I wonder whether or not it is something technically different that our team does, or if the patients are being kept on Plavix—I know they are on Plavix for six months and then they are on aspirin forever. I cannot really answer the questions because I am not the person who is directly handling the surgery. At the same time, it is a very good question.

DR. PATEL: Thank you.

13. Sara Syndrome

DR. HAROLD L. REKATE, MD

I'm going to try to do this rather quickly because it's been, for me, an amazing trip to get to this point of discouragement. I'm overwhelmed. And I'm so glad that I don't suffer from these things. The deeper I tread into it, the harder it becomes. But there's a huge amount of courage in the people that have this condition, at least, the ones that I treat – they're fighters, they're looking for help. And I'm amazed by them.

The syndrome: I think that the biggest challenge we seem to be fighting, is the fact that nobody sees it, because they haven't seen any black swans lately. There appears to be an absolute denial that this syndrome exists, in the vast majority of physicians and particularly among neurosurgeons.

We have two things. The first problem is how to define this entity. Let's call it a syndrome of some sort- it has so many different parts of it. What are the essential parts, and which are the parts are "camp followers", cause and effect.

The definition is difficult. It is syndrome, a group of symptoms and physical findings that consistently appear to occur together. And it's usually a genetic condition. Although, in my back yard, it's considered a social syndrome. For the purposes of this lecture, I call it "Sara syndrome" because I didn't have any idea of the nature of the problem when I first started seeing patients with hypermobility connective tissue disorders coming through my office, that were so broken. The first person in whom I recognized the syndrome was a Sara.

When I talked to Dr. Francomano, she said, "Well, all of my patients have all of these things." And so I think I have seen the word EDS 3+ or something like that or plus as a name. I would like to call this the Fraser Henderson syndrome, because I am sure that he is the first person to recognize the relationship of the cranio-vertebral junction to the syndrome of POTS - other aspects of dysautonomia- and the other comorbid conditions that we're talking about today, the list of which keeps getting bigger. (**Fig 1**)

The CSF 2014 Consensus report refers to this cluster of symptoms, as the "cervical medullary syndrome".[1] The problem with using the term cervical medullary syndrome is that it presumes a cause-and-effect relationship, a relationship that will have the skeptics dig their feet in deeper. If we could find a more general name for the syndrome, it would be better. But we need more data. This presentation will provide several instances that might direct us.

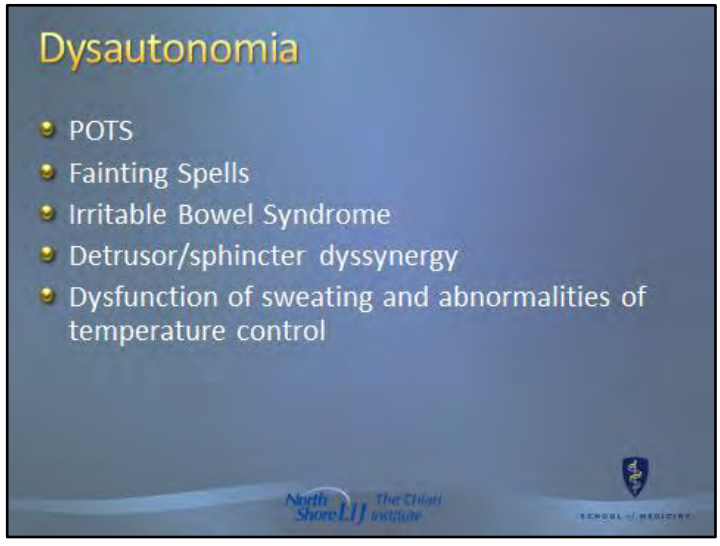

Figure 1

So what is this relationship of Sara Syndrome to Chiari malformation? This has come to me in a relatively fast-paced way- the recognition of this relationship of Chiari I with EDS was made by Dr. Francomano, Dr. Kula, and Dr. Bolognese.[2] I'm leaning to say, that I don't entirely agree.

The recognition of Chiari with cranio-vertebral instability and ventral compression of the brainstem was the next step along the way. But all of the patients that were evaluated for that condition had tonsillar descent. They usually had a minimum degree of tonsillar descent, which Dr. Malhotra called LLTs or low-lying tonsils.[3] LLTs usually would not generally be regarded by radiologists as being Chiari malformations. The critical paper by Milhorat et al did specify that they had low-lying tonsils, and not really Chiari malformations. Nevertheless, I think, that the inference that LLTs should be treated as Chiari malformations led to suspicion and skepticism.

The next step in this process was the recognition of the importance of craniocervical instability with dysautonomia, the credit for which recognition I give to Dr. Henderson. When I first came to the Chiari Institute, I was saying, "Where did this syndrome come from?" And the more I hear the conversations, and the more I see these patients, the more completely convinced I am that that dysautonomia is one of the key mechanisms involved.

So the question becomes, “Is the tonsillar descent an incidental finding leading to the syndrome, or not?” The more I delve into this, the more convinced I become that the length of the cerebellar tonsil has a wide spectrum among normal people. And, indeed, the more I think that the tonsillar descent is an incidental finding which has led to the recognition of the instability of the cranio-vertebral junction.

So the following relates to a patient who the patient demands re-exploration of the analysis. At the age of two, she had undergone a kidney transplant for mesangial sclerosis, wherein the renal cells become replaced by mesangial cells. Those afflicted usually die by the age of four. She's was EDS hypermobile. She had severe headaches, which were of a mechanical nature; so that, if you held her head up or you put her in a collar, she was better. She had excruciating abdominal pain. She's lost a huge amount of weight. She had a feeding tube for a long time. She has chronic constipation. There was tonsillar descent, a small Chiari malformation. She was the first person that I recognized, who had the syndrome that we've been seeing with Chiari malformation, but whose radiological findings definitely met our criteria for instability: over a 9mm Grabb-Oakes measurement[4] a very acute angle of her retroflexed odontoid, causing a pathological basion axis interval (pathological horizontal Harris measurement).[5,6,7]

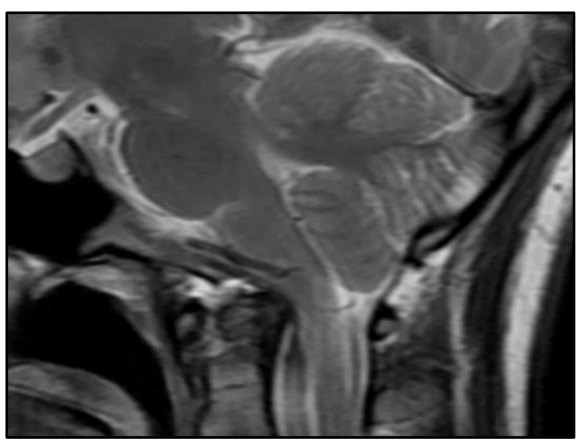

Figure 2

This patient had the Sara syndrome. (**Fig 2**) There is a small Chiari malformation, but more remarkable are the radiological findings of craniocervical instability (the pathological Horizontal

Harris measurement, and basilar invagination (the hyper-kyphotic clivo-axial angle/ retroflexed odontoid).

And I fought with myself about whether she should be undergoing surgery. But she was absolutely miserable, had no life, almost never left the house, and had dropped out of college. So after a stormy surgical course, complicated by mast cell activation syndrome- and Dr. Maitland is helping with this- she's now eating, she's gained a fair amount of weight, her abdominal pain is much improved, she has had no syncopal episodes since discharge. It's only been a 2 months since discharge, so it's too early to give a clear follow-up. This patient exemplifies the Sara Syndrome, but her story may have less to do with Chiari malformation than with the cranio-vertebral instability issues.

This seminal work by Milhorat et al, brought attention to the fact that many patients who had been treated for Chiari malformation, and failed, had an underlying condition of EDS.[8] In fact, 12.5 % of the Chiari patients treated at the Chiari Institute were diagnosed with hypermobility conditions, such as EDS. Milhorat et al, 2007 demonstrated that many Chiari patients had hypermobility disorders, and that craniocervical instability was a major determinant in their clinical presentation. (**Fig 3**)

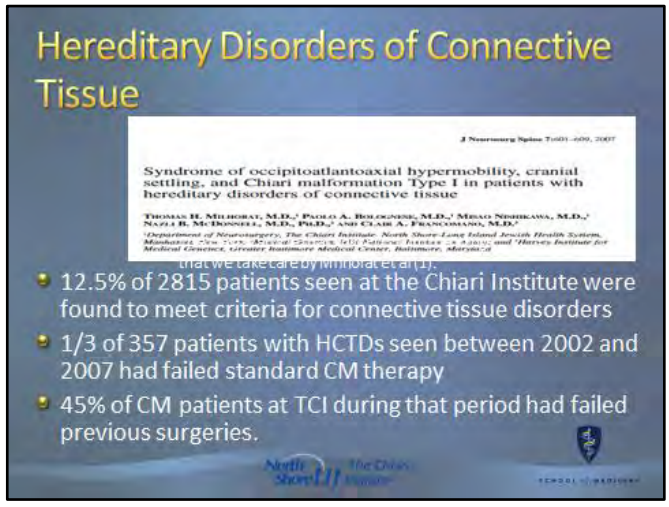

Figure 3

Is it not likely that we could focus on what really is the problem; and that is the instability of the cranio-vertebral junction, rather than the Chiari? These patients with the Sara Syndrome- which Dr. Henderson calls the cervical medullary syndrome - all have EDS. I give credit to Dr. Henderson, who said that the majority of the patients he saw had less to do with low-lying cerebellar tonsils, and more to do with issues of ligamentous instability. It dawned on me that he meant that this problem isn't so much the Chiari problem, but rather the problem of cranio-vertebral instability.

These syndromes – CCI, EDS, Dysautonomia, pervasive pain / fibromyalgia and Chiari malformation – substantially overlap in terms of clinical presentation. However, in contradistinction to the above patient history, the Chiari malformation does not necessarily belong etiologically in this grouping of diagnoses. The Sara syndrome can arise independently of a Chiari malformation, and should not therefore be confused with Chiari malformation. So I would like to take Chiari out of the Venn diagram. The Chiari malformation does not necessarily belong etiologically to this grouping of disorders, despite the similarity of some of the presenting clinical findings. (**Fig 4**)

The confusion of Chiari malformation and craniocervical instability is a fundamental issue, and problem. As soon as we can jump across that hurdle, then we may have less trouble with our skeptical colleagues.

As an aside, I wanted to mention new work on the link between dysautonomia and the immune system, from Kevin Tracey - director of the Feinstein Institute at Hofstra. Tracey gave up neurosurgery to cure the world. His work has been on the autonomic nervous system's control of the immune system.[9] The stuff that he does is brilliant. I had no idea of the relationship of dysautonomia directly to central nervous system control of the immune system. It's truly remarkable. Perhaps a little caution is appropriate because he's invented a new percutaneous implanted vagal nerve stimulator. However, I think it might be relatively simple to test the hypothesis some of the manifestations of dysautonomia would be helped by vagal nerve stimulation.

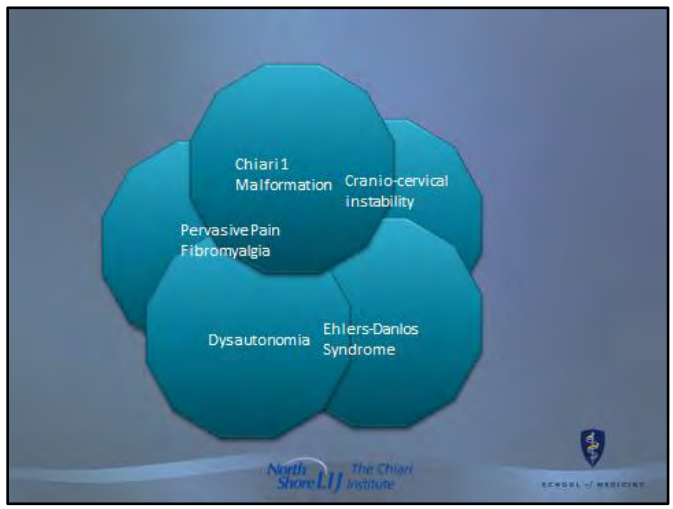

Figure 4

So what's going on with the Sara syndrome? It's a genetic condition with autosomal dominant transmission. Though there are very few males in my series, it has near complete penetrance among females. It appears to be in part an inflammatory condition: many of the patients have mast cell issues; but the systemic markers of inflammation are either high normal, or just barely abnormal. They also have compression of the anterior brainstem. Under ultrasound control, during surgery, before opening the dura, one can see the odontoid process and the anterior brainstem bouncing off of each colliding with each cardiac function. Whereas, the MRI scan may have appeared that they were not touching.

So we have three pairs of identical twins with EDS 3+, with the entirety of the syndrome. The 41-year-old pair both has instability at the cranio-vertebral junction, based on the established metrics,[10,11,12,13] both had major bowel resections, because they did not have any peristalsis at all. And one is waiting -- she's been four years on total parenteral nutrition because she has no working gut at all- for a transplant.

The two other cases, however, are more interesting. One is a 17-year-old pair of males. The other one is a 31-year-old pair of females. Within each pair, one is completely disabled by this whole syndrome, with the POTS; they have G tubes, and ports to self-administer intravenous fluids so that they can get out of bed, but they can't do anything else. Whereas, their siblings have dislocating or subluxing hips, subluxing knees, dislocating elbows; but they don't have the Sara syndrome, and they do not meet the criteria for cranio-vertebral instability.

Those two pairs support the concept of the importance of the cranio-vertebral junction in the etiology of this syndrome. I've been in contact with Professor Ashley-Cook, who agreed to a protocol for the genes to be sequenced to take a look at how they're dealt with. We believe now that the brainstem does have a major effect on dysautonomia, and some of the co-morbid conditions that we have discussed. We have to define

the study group, and to rename the condition that encompasses this aggregate of findings.

Discussion following presentation

UNKNOWN: In genetics we have this very well recognized principle of variable expressivity. The way I think about this is that the patients have an underlying hereditary disorder of connective tissue, and there are different complications that are associated with that underlying hereditary disorder of connective tissue, similar to what we see in neurofibromatosis.

Some people have neurofibromas, some people have cognitive impairment, and some have Lisch nodules. And they have different combinations of those things. So when I look at these patients, they're the furthest end of the spectrum, the most severely affected by this condition, that we call the hypermobile type of Ehlers-Danlos syndrome.

They have relatives that have joint hypermobility, but do not have these manifestations or they may have one or the other of them. And I think it's going to be tremendously interesting to try to understand what it is that causes a person to have the whole full Monty, and other persons to have very few of the manifestations. But I don't think it's a separate entity. I think it's just the spectrum of hypermobile Ehlers-Danlos syndrome with neurologic and immunologic complications. I don't really believe we need another name for it.

DR. REKATE: I completely and absolutely disagree with you.

If there is a therapy that makes a difference in these people's lives -- and I can promise you that I have, at least, a dozen now patients who have appear to have made substantial improvements. I do believe that, at least at this moment, craniocervical fusion has helped these people live a relatively normal life.

UNKNOWN: I don't disagree with that. I absolutely believe that neurosurgical intervention is extremely helpful for some of these patients. That doesn't say that it's a separate entity from the underlying hereditary connective tissue disorder.

DR. REKATE: Let's look at it the way the Institute of Medicine would look at it, especially with ICD-10, which demands that medicine have a diagnosis code and a treatment code. And they have to be paired.

In diagnostic terms, you're a “lumper”, and I'm a splitter. But there's a reason for splitting, which is that a precise diagnosis can inform the treatment plan, which is the intent of the ICD 10, to establish diagnosis/treatment pairs.

UNKNOWN: But you can use craniocervical syndrome, right now ICD-9 code 723.2. I don't know what the conversion is to ICD-10. And diagnostic code is a justification for stabilization of the craniocervical junction.

We code patients for the underlying hereditary disorder, and then whatever other complications are associated. It might be anxiety, or constipation, or urinary frequency or urgency. But you code for all of those and you treat for the ones that are appropriate in that patient.

DR. REKATE: We'll agree to disagree.

UNKNOWN: Okay.

DR. REKATE: I think, we're all worrying is to keep an open mind about these things. And the more you try to make a separate diagnosis of something; the concern is that, sometimes you get led astray.

I have an interesting patient. I have a 43-year-old, he was a previous fireman. He was admitted to one of the local hospitals with intestinal obstruction. He had surgery. They thought he might have a tumor, but found intraoperatively there was absolutely nothing there, and they closed him up. And he went to a GI specialist, a bowel guy to try to get his bowels working; and he had a great deal of difficulty with that.

I happened to see him. We worked him up for a variant of myasthenia gravis or an antibody to the ganglionic acetylcholine receptor. And we tested him on this, and he didn't have it. But in any event, I gave him Mestinon, which is a cholinergic stimulus; and he started moving his bowels, and he was a hundred percent better, which was great. I mean, it looked like we had had some idea about the whole thing.

Anyway, as time went on, he started to break through this; and he, all of a sudden, became very sick again. And what he had was impotence, orthostatic hypotension. And he became obstructed again, and he was taking more and more Mestinon. It was not working. And we tested him again. He did now have the ganglionic antibody; and he also had an antibody to the regular acetylcholine receptor, like myasthenia gravis. But he didn't have myasthenia gravis. It was looking more like an Eaton-Lambert syndrome, which presents with lower limb weakness, gastrointestinal stuff, impotence, and dry mouth. So we put him on prednisone. Inside of two weeks he was back. Good sexual function, he had no orthostatic hypotension anymore, and his bowels were moving again. And he's continued to do fairly well.

So this is an autoimmune syndrome that shares many of the features that we've talked about with EDS patients; but he's not hypermobile. He has the bowel problems, these symptoms are very general, and we may be dealing with multiple disorders.

I mean, we deal with ALS. It was always treated a single solitary diagnosis; and now we really understand that there are probably seven, eight, maybe more diseases here. We at once wanted focused treatments. But if we get too certain about things, we end up maybe getting down the road and treating people in a certain way, when we really may be dealing with two or three or four different diagnostic categories. So you just learn a lot by listening to -- and individual patients, I guess as we've heard here many times, can teach you a lot, even if it's one patient that you try to understand.

UNKNOWN: I have a comment about that last comment and the argument. Even though it's in its infancy, there are statistical ways to begin to validate syndromes. It's never been done before. It's always been done by observation.

And the most obvious ones, the herniated lumbar disk with nerve root compression, I mean, they take thousands of years for people to figure them out; but once they're figured out, everybody recognized them.

There are techniques now known as cluster analysis, derived from Warren Turgeson's ideal type analysis. And these are statistical techniques that allow you to do just

what Hal brought up on his first slide, to define the syndromes, to determine which ones actually are aggregates of reproducible syndromes. And I think this is a field just crying out for it.

I brought this up in our meeting the other day, and I'm exploring it with some of the biostatisticians in the Hopkins undergraduate school and out at Berkeley right now to see.

This is something I know little about, except the papers I've read, and I'm looking for experts that might be able to help us.

UNKNOWN: In March of this year there was a whole issue of the American Journal of Medical Genetics that was dedicated to this exact topic. There were probably seven or eight different articles talking about the relationship, coexistence or comorbidities of hypermobile Ehlers-Danlos syndrome, all the neurologic complications that we've been discussing today, mast cell activation disorder, and gastrointestinal complications, dysautonomia – all of these comorbidities have been recognized and published in the genetics literature.

So I feel like we're kind of trying to reinvent the wheel in a way by renaming this thing. I mean, the whole field of genetics has been really looking at this very closely for quite some time now. So -- that's all I have to say.

UNKNOWN: When you say the whole field of genetics, the majority of geneticists still do not understand Ehlers-Danlos syndrome hypermobility type. When we find out the name of a geneticist who really understands what's going on, I write it down in my notebook because there's so few of them.

DR. REKATE: I'll grant you that.

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14. Cardiovascular Instability in Chiari and Related Disorders

DR. PETER C. ROWE, MD

Thank you. It's a pleasure to be here with everybody again. My talk will complement some of the things that Dr. Henderson was discussing, maybe digging down a bit deeper into some of the issues. I'm going to start with an overview of the common orthostatic intolerance syndromes, and then go into greater detail regarding the association with Chiari malformation in the literature. I'll talk about improvement in the autonomic symptoms following surgery. There isn't a ton of data on this, but there are a few papers that are fairly difficult to argue. I'd like to end with some clinical observations on patients who have improved, in terms of the postural orthostatic tachycardia symptoms, between pre- and post-surgical testing after management of ventral compression of the spinal cord in the cervical region.

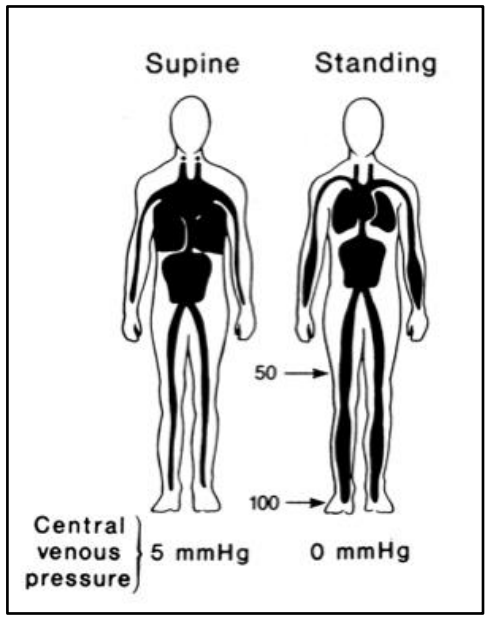


Figure 1 – pooling of blood volume into the lower extremities.

When we refer to orthostatic intolerance we are referring to a group—and it's important to think of it as a group— of clinical conditions, where symptoms worsen with quite upright posture and then are ameliorated, although not usually completely abolished, by recumbency.

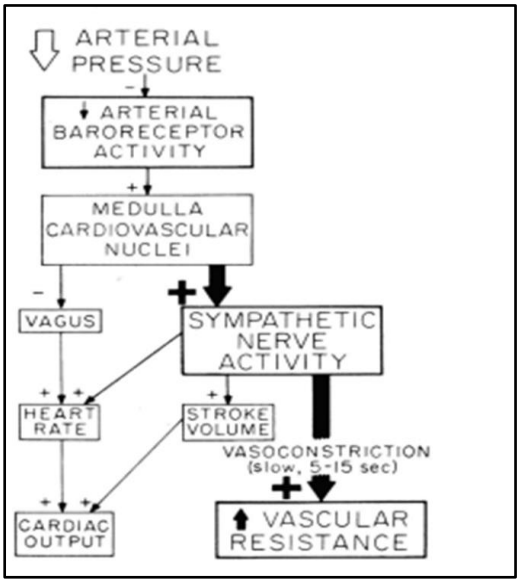


Figure 2 - The normal physiological response to orthostatic stress (Adapted from Rowell LB, 1993)

Phil Low, part of the big autonomic group at the Mayo Clinic, published this diagram **(Fig 1**) in his textbook about the changes that we are facing, in terms of distribution of blood flow. There's a 500 to 750mL drop of blood volume into the lower half of the body. This diagram doesn't even really show very well just how much is in the splenic circulation, but up to a quarter of the blood can be sequestered there at times.

When we have that much blood in the lower half of the body, the normal response to physiologic stress is to have a drop in arterial pressure, unloading of the arterial baroreceptors, an increase in sympathetic nerve activity that leads to about a 10- or 20-beat increase in

heart rate initially, and improvement in stroke volume.

But the big change is the sympathetic mediated vasoconstriction: That is responsible for shifting the blood back up to the brain adequately enough so that we can keep thinking or even speak. When that doesn't occur properly, you get this group of symptoms, which recalls Dr. Francomano's comment about things that might count as a positive review of systems. These are all the features that we can see in the syndromes of orthostatic intolerance. (**Fig 2**)

Here are features that usually are attributed to reduction in cerebral blood flow. (**Fig 3**) On the right is a group of symptoms, such as orthostatic intolerance, and dyspnea, which are probably related to a reduction of blood flow back into the thorax, along with some effect on stretch receptors in the vessels of the chest, and then many of the others that result from the hyperadrenergic consequences of the body trying to adapt to too much blood in the periphery.

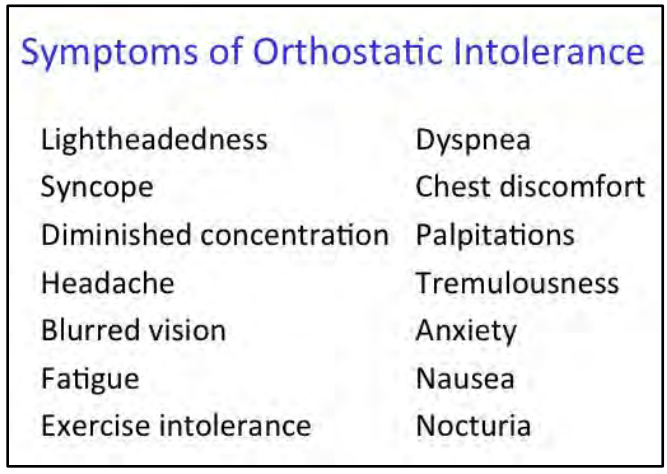


Figure 3 - Symptoms that arise as a consequence of orthostatic intolerance.

Chest pain is really common. These patients often report palpitations, they're often shaky and anxious— anxiety being much more overrepresented in the patients with orthostatic intolerance than you'd expect by chance. Interestingly, the techniques that we use to trigger orthostatic intolerance and syncope in the laboratory using isoproterenol as a stimulus during tilt-testing were used in the '60s by psychiatrists to trigger a panic attack. Thus, there may be some physiologic reasons for the increase in anxiety in these patients.

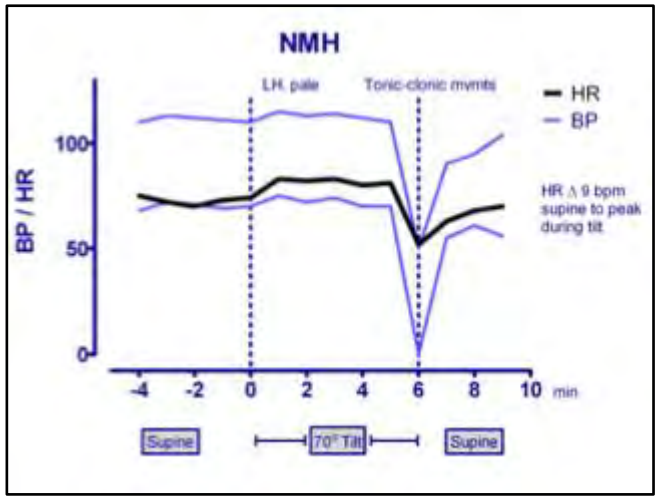


Figure 4 - There are two common forms of orthostatic intolerance, POTS and neutrally mediated hypotension. These are demonstrated on the tilt table.

There are several common forms of orthostatic intolerance. One is postural orthostatic tachycardia syndrome or POTS, which requires, in adolescents, a 40-beat increase in heart rate from supine to standing; in adults, a 30-beat increase or a heart rate above 120 is required. You must also have reproduction of the typical orthostatic symptoms within the first ten minutes of standing tests or head-up tilt. (**Fig 4**)

There is also a form that we call neurally mediated hypotension. It's synonymous with vasovagal syncope, neurally mediated syncope and neurocardiogenic syncope. We like the term neurally mediated hypotension, because not all of the patients who have this pattern on tilt-testing are actually syncopal in day-to-day life. We would often call a referring physician back, saying, "Your patient has neurally mediated syncope"; and they would respond by claiming their patient had never fainted. So in order to mediate any confusion caused simply by terminology, we've just begun referring to this as neurally mediated hypotension. This phenomenon, seen in Figure 4, is essentially a process where the heart rate doesn't rise until, at the six-minute mark, there's a big reduction in blood pressure down to about 50 systolic, slowing of the heart rate, which would be maladaptive to remaining upright. This is a characteristic pattern of vasovagal response— a pattern thought to be the most common cause of syncope at any age. As we've been saying with some of the other syndromes discussed today, it is more common in women, younger people and in those who have a low normal starting blood pressure or low blood pressure. It can be triggered by infection. Family members are often affected and that may be, in part, because of the Ehlers-Danlos syndrome (EDS) connection.

Typically, in the past, the routine physical exam and the laboratory tests for these folks have been normal and the hypotension would not be detected on the usual two- or three-minute orthostatic vitals that are often done in clinics.

Our median time to hypotension, on tilt-testing for our chronic fatigue syndrome patients, is 29 minutes. They are symptomatic all the way along, but it's only after about half an hour that you see the drop in blood pressure. One of the issues that has been known since about the 1920s is that fatigue can be present for up to 72 hours after initiating one of these episodes, after the reflex arc is triggered.

The thought is that with upright posture or tilt, you see a reduction of venous return, which drops blood pressure. There is an increase in catecholamines in response and, typically, epinephrine levels go sky high in people with recurrent syncope, compared to controls. Then, in the setting of an under-filled ventricle, where there is a lot of pooling of blood in the periphery, the increased catecholamines seem to trigger a reflex pathway, whether from the left ventricular free wall, mechanoreceptors, or from some baroceptor response. In the end, you get a relative increase in vagal effect and a withdrawal of sympathetic tone, resulting in a drop in heart rate and vasodilation, and if the person doesn't sit down or get down to ground, they are at risk for hypotension and syncope. (**Fig 5**)

POTS, on the other hand, has been more recently recognized; although it was described in the medical literature as far back as the Civil War era, when soldiers who were too fatigued to keep fighting were thought to have an irritable heart or ef-

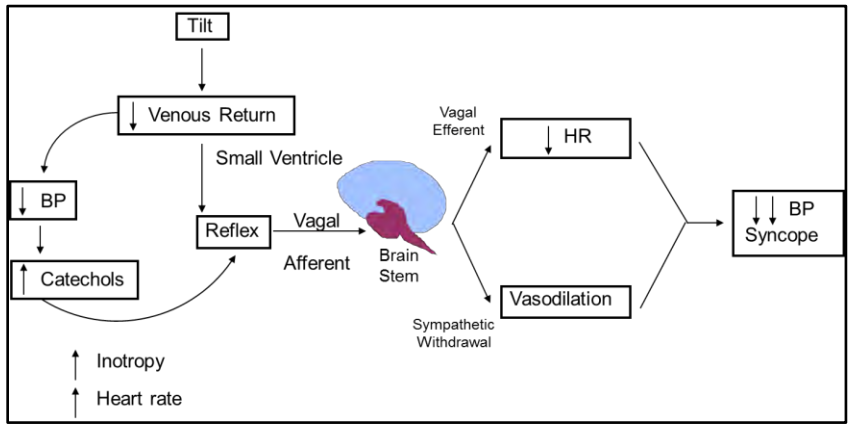


Figure 5 - demonstrating the physiology of vasovagal syncope. (Adapted from Chang–Sing P, Cardiology clinics, 1991)

fort syndrome. Osler called it neuro-circulatory asthenia.

In POTS, the female-to-male ratio is four to one. It is uncommon under the age of ten. We see a lot of the young girls developing this as they reach puberty; and so, again, we see ourselves talking about the hormonal effects on circulation and how that may be playing a role—though the mechanisms have not been nailed down.

Onset can be gradual, or it can occur —importantly for this audience— after prolonged immobilization or surgery. It can also occur occasionally after immunization. There are a couple of reports that this follows the HPV vaccine. Certainly not a reason to stop giving the vaccine by any means, but there has been a big increase in the recognition of this in the last 10 to 20 years, therefore possibly an increase in its true incidence.

The pathophysiology is heterogenous. Some centers measure norepinephrine levels during upright tilt, and then can stratify based on what the norepinephrine is doing. As I mentioned, epinephrine levels typically go up in the syncopal patients; norepinephrine in the POTS patients. So, if you have a norepinephrine level above 600, that's thought to be the dysautonomic or neuropathic form of POTS - due to a patchy loss of sympathetic fibers in the legs. On the other hand, the central hyper-adrenergic form is with a norepinephrine level above 1,000. My caveat here would be to say that all forms of orthostatic intolerance are hyper-adrenergic to some extent; and so these debates about whether or not people have the hyper-adrenergic form are, to some extent, quibbling.

One of the curiosities of these conditions is that an individual's blood volume is 10-15% below where it would be predicted to be, given that individual's age and body mass index. The body also will not compensate for this; it will not fix the problem. We're not sure why. You can see elevated renin-to-aldosterone ratios. Joint hypermobility is common in the POTS group. Deconditioning can become common based on the level of disability. Also, about a year ago, Dr. Milner's group at the NIH showed an association between mast cell disorders, fatigue patients, hypermobile individuals and those with POTS.[1] We've been rushing to catch up to that observation for a while.[2]

Dr. Henderson mentioned Inge De Wandele's studies from Belgium. (**Fig 6**) This group carried out a huge comparison of people with EDS and controls.[3] The darker line represents EDS patients with the hypermobile form. The panel compares the EDS hypermobile type (darker line) with controls (lighter line); and you can see the vast differences between the hypermobile EDS patients and those healthy controls.

This diagram synthesizes a lot of the thinking and the literature on the pathophysiologic influences on orthostatic intolerances. In all forms of orthostatic intolerance, patients experience an increase in peripheral pooling or some defect in their ability to vasconstrict and direct the blood back up to the heart. There is a re-

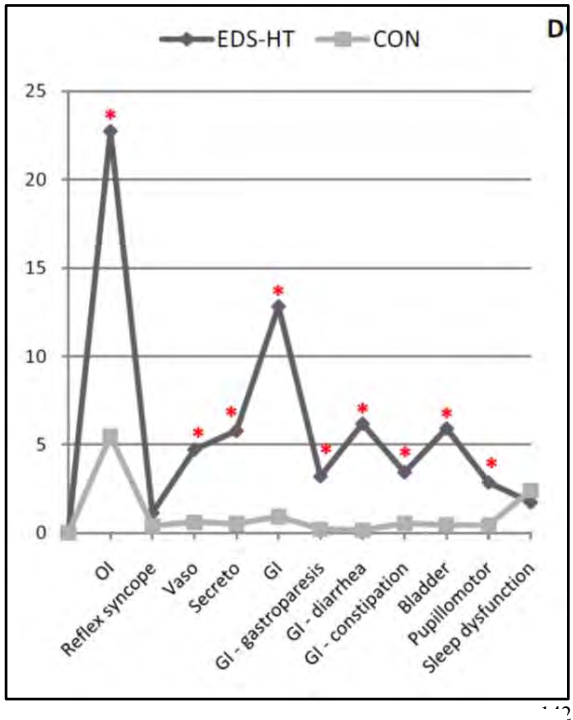


Figure 6 - Comparison of patients with the hypermobile form of EDS with controls, demonstrating the large number of dysautonomic findings that afflict the EDS-HT population.

duction in intravascular volume, and that can always be made worse by anything that's of dehydrating influence on them, day-to-day. In response to orthostatic stress, we observe a big sympatho-adrenal response, bigger than would be expected for healthy people. (**Fig 7**)

David Goldstein at the NIH has proposed that if the norepinephrine increases more, relative to your epinephrine level, the subject is better able to vasoconstrict, and to preserve blood pressure; those subjects, then, would represent the POTS phenotype.[4] Whereas, if there is more epinephrine release, there will be skeletal muscle vasodilation, which results in a drop in blood pressure and fainting. Subjects who have POTS early in the tilt test can go on to drop their blood pressure later. These issues must be considered along a continuum, rather than being absolutely distinct.

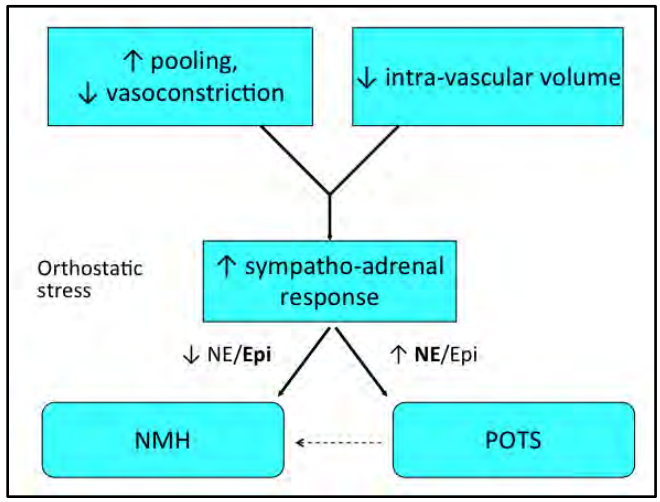


Figure 7

At a clinical level, one of the things we look for is this dependent acrocyanosis. These images are of a college student who had to withdraw from college because of the severity of her fatigue and POTS. (**Fig 8)** The left panel is her hand hanging down during a standing test; this picture was taken about three minutes into the test—a normal hand is placed behind hers, for contrast. On the right, fingers were pressed against the area of acrocyanosis; 5 to 7 seconds afterwards, showing no capillary refill. If our ICU patients had this kind of change, we'd be all over them with dopamine drips. These patients have something very wrong with their circulation.

Figure 9 illustrates one of the bad things that can happen after very good surgical corrections. (**Fig 9)** After patients are in bed for two weeks, what happens to them physiologically? These are studies from NASA, where they tried to replicate the effects of zero gravity on circulation. They had their so-called volunteers in bed for 220 days. Extraordinary. I don't know what we can get that past an IRB anymore. What I want to draw your attention to is the amount of plasma volume loss in the first two weeks or so, where they would lose up to 15% of plasma volume in that time just from being in bed. That can be attenuated if they use one of those leg bicycle techniques: exercise helps prevent this. Complete inactivity can be a horrible trigger to these orthostatic disorders.

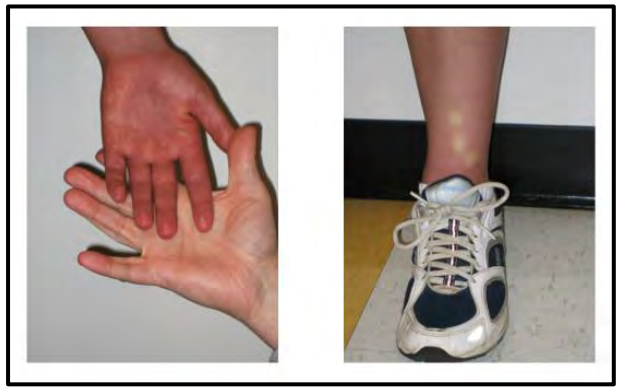


Figure 8

Okay. Let's switch a bit to the literature on Chiari malformations and syncope. What is the relationship of dysautonomia to Chiari malformations and syncope? I want to start with a couple of the things that Dr. Henderson had mentioned. The observation of syncope, even as a presenting feature of Chiari malformation, has been around for several decades. The first paper was published in 1982.[5] There was also an early case series in the early 1990s.[6]

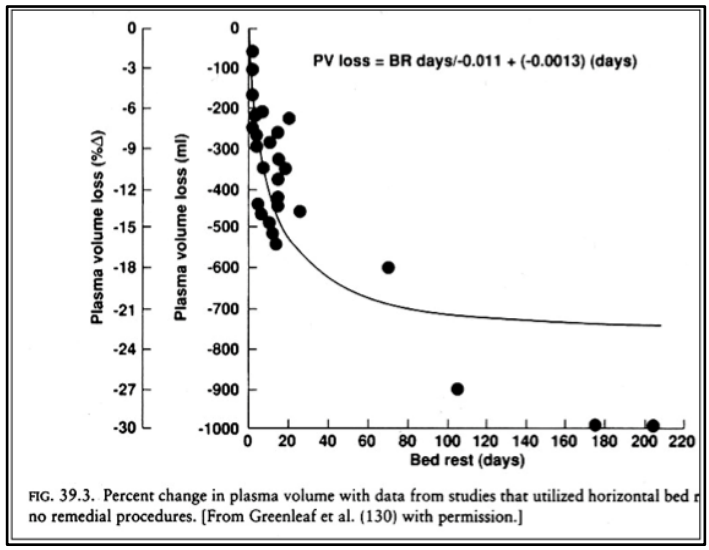


FIG. 39.3. Percent change in plasma volume with data from studies that utilized horizontal bed r no remedial procedures. [From Greenleaf et al. (130) with permission.]

Figure 9 - the loss of plasma volume that occurs in the patient at bedrest over time.

More recently this paper was published, describing a 42-year-old who had progressive occipital headache, nausea, vomiting, some associated fatigue.[7] I think, Dr. Kula, your group with Dr. Milhorat discussed fatigue being present in about two-thirds of the Chiari patients. The patient from this study, however, was having recurrent syncope several times per week. The syncopal episodes were preceded by tachycardia, palpitations, and the features discussed earlier including some diplopia, which we don't typically see. She was fatigued for several hours afterward.

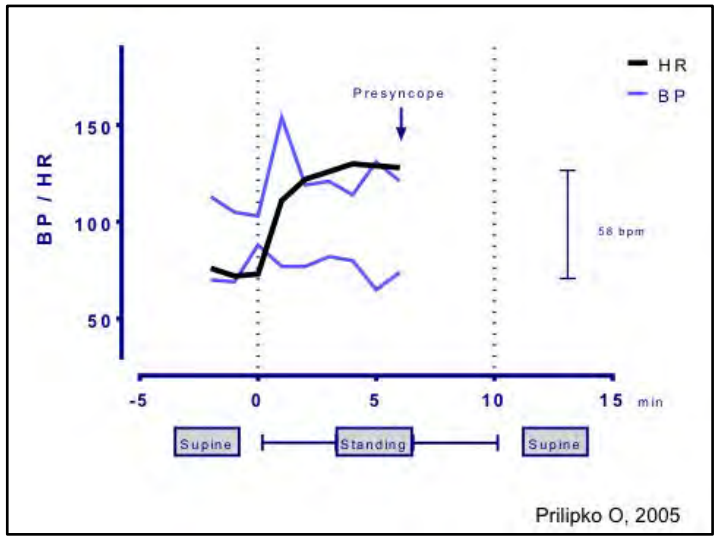


Figure 10 - the loss of plasma volume that occurs in the patient at bedrest over time**.**

The Prilipko team mentions that the neurologic exam was entirely normal.[8] I'm not sure that we can take that completely at face value; the other cardiovascular studies didn't show much. Because of the diplopia, the subjects underwent an MRI. In any event, the investigators also carried out a standing test, which found that the patient was able to stand for about six minutes. (**Fig 10**) The blue is the systolic and diastolic blood pressure.

The thing I wanted to draw your attention to is the black line, which is the big increase of 58 beats per minute in heart rate with simple standing. Notice that this patient's heart rate was around 140bpm, which most of us have to work pretty hard on a treadmill to reach. This was a spontaneous event within 6 minutes. The associated MRI findings

revealed a Chiari malformation. (**Fig 11**) Surgical decompression of the Chiari resulted in complete resolution of the subject's syncopal episodes and other symptoms.

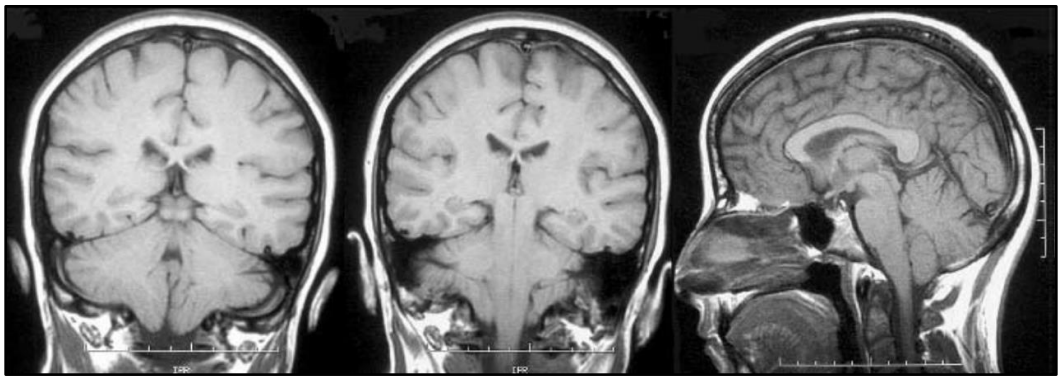


Figure 11 - The subject was found to have a Chiari malformation. (T1 weighted coronal and sagittal MRI)

The investigators' comment was that the patient's syncopal episodes, gait and unsteadiness, and visual and sensorimotor symptoms all disappeared after surgery and remained absent at the three-month and one-year postsurgical follow-ups. Postoperatively, they repeated the standing test (**Fig 12**). Side-by-side slides compare the first standing test, where she developed presyncope at six minutes with the follow-up study, after treatment, showing that this patient was able to stand well beyond ten minutes with only a 17-beat increase in heart rate, compared to a 58-beat increase prior to surgery. So, in this instance, the Chiari correction was associated with a marked improvement in the autonomic symptoms and in the objective measures of circulatory control.

It is important to recognize that the Chiari malformation represents a broad category, so that generalizations should not be made. People have looked at the mechanisms for syncope in Chiari malformation. One possibility is vertebrobasilar artery compression, due to a transient increase in intracranial pressure with a Valsalva maneuver. We also know about sneeze and cough syncope— which occur through this neurally mediated reflex mechanism.

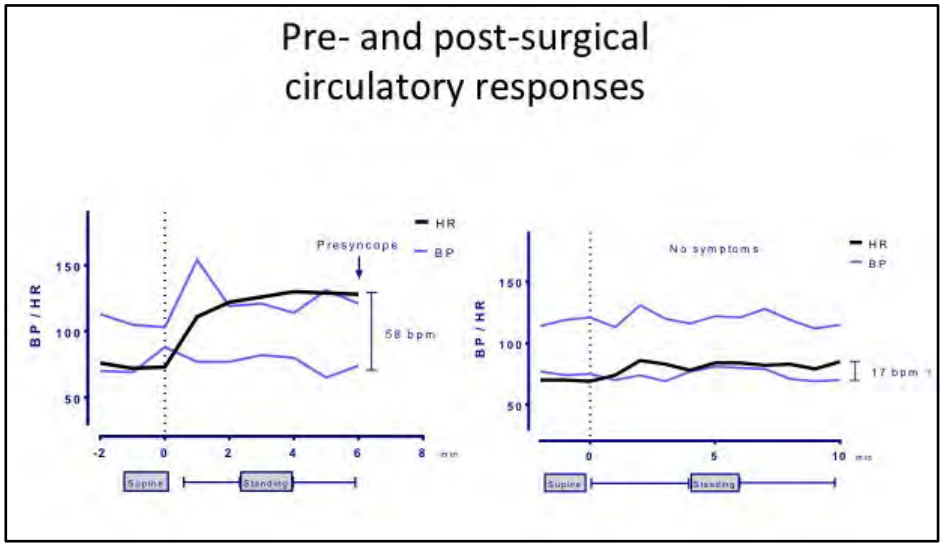


Figure 12 - Following the Chiari decompression, the POTS and the syncopal events resolved.

The oth-

er thought is that compression of midbrain and the ascending reticular systems result in syncope. And, Dr. Henderson should perhaps extend that proposal to the effects of deformative stress on those areas. Deformation of the brainstem may result in possible compression of cardiorespiratory centers or the sympathetic structures and their afferent or efferent pathways.

Krassioukov, a specialist in spinal cord injury out of Vancouver, investigated the latter part of this concept. He provides a review of the detailed mechanisms of autonomic dysfunction in people with spinal cord injury that, I believe, also applies to the kinds of things we are discussing here today.[9]

In 2001, a paper came out from Buenos Aires. The senior author of this paper is now at the autonomic group at the Mayo Clinic.[10] The group had a patient with POTS and syringomyelia whose symptoms did not require surgery, but responded to medication. I just want to share that history with you.

The patient was a 45-year-old female, whose Chiari was identified at age 33 when she came in with headache after cough and sneezing. She had some dysphagia and unsteady gait, and a syrinx that extended from C3 to T12. She initially had two syrinx-to-subarachnoid shunts placed as well as a decompression of the Chiari malformation. Initially, her headache responded and she did well for a few years. Then at age 41 – so four years before Dr. Nogués and his team treated her – she started experiencing palpitations, shortness of breath, nausea, light-headedness, and a tendency to fall which triggered some anxiety and fear. These symptoms were happening upon standing.

Upon examination, the only abnormality was tachycardia; the general assumption by many of the physicians who saw her was that this was psychogenic in nature. So the group repeated the MRI, and the syrinx had collapsed. She had a persistent Chiari malformation, and they argued whether that could be contributing. They also found some myelomalacia. Then they performed the tilt table test; after about 15 minutes, she developed syncope. They treated her with 400 cc's saline, and that normalized the blood pressure. This was before treating her with Florinef and atenolol, so they used medical management of these symptoms. The results of the repeat standing test, showed improvement in function.[11]

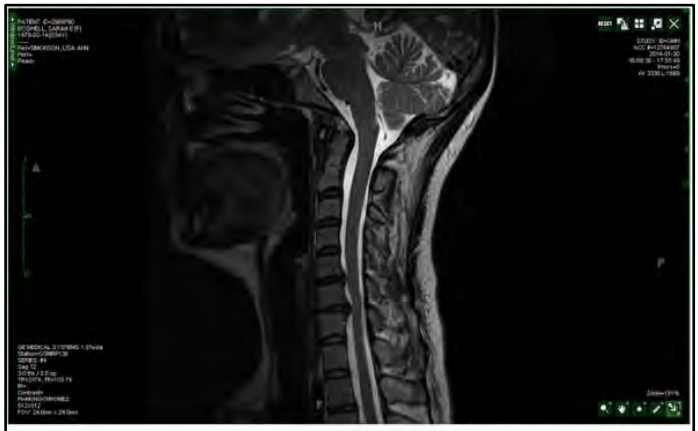
She was able to get back to her daily activities. So not all of these patients need surgical correction, but the symptoms warrant further investigation. She had, however, been pretty healthy. She was working initially for the CIA, and then for the State Department. She developed this fatiguing illness while she was stationed in Madrid at age 29. The symptoms were the familiar ones: she has constant fatigue, light-headedness several times a day, frequent presyncope, palpitations. She described her shoulders hunching up when she was walking, and a burning in her legs when standing, which kept her frequently in a recumbent position. She had paresthesias, more on the left than the right; electric shock sensations in her arms; and some difficulty swallowing.

When she was worked up at our institution on a prolonged inpatient stay, she had hyperreflexia at every examination. The EMG and nerve conduction studies were normal. The MRI of the brain and her entire spine showed what was termed mild degenerative disc desiccation, extending from C3 through C7. Most people, subsequently, in their notes, would say the MRI was unremarkable.

They did tilt-test her and she had evidence of POTS. Her heart rate went up from 65 bpm to 126 bpm at ten minutes, again a pretty remarkable increase.

But the treatment of the POTS by a very good person in Baltimore did not lead to improvement. So, over the next six years—and that is a long period of time for anybody, but especially for someone who had been dysfunctional— she had progressively worse fatigue and orthostatic intolerance. She became unable to work early in this process, and had to move home with her parents on whom she became dependent. She would use a wheelchair for any trip out of the house, because even a trip to the doctor would make her really light-headed and she would need two weeks to recover from that. She spent, by her estimate, 95 percent of the day reclining, which was not helping her orthostatic intolerance any either.

I was asked to take a look at her records by a family friend, and was struck by the kind of presentation we see in this group a lot. We arranged to have her internist get a repeat MRI. (**Fig 13**) I think you can see, even from afar, that she really had quite a narrowed cervical canal. She had 9 mm of canal diameter at C5-6; and at C6-7, just 7 mm. She also had an abnormal clivo-axial angle.



Repeat MRI 2014: 9 mm canal diameter at C5-6, 7 mm at C6-7, clivo-axial angle=124°

Figure 13

So I sent her to a spine surgeon in Baltimore who was interested in these problems. He identified, in addition: an absent gag, some reduction in strength in the triceps and the wrist flexors. By the time we saw her, she had a couple of beats of clonus at the ankles. The Baltimore surgeon recommended fixing these big disc bulges at C5-6 and C6-7, one with disc replacement, the other with a fusion.

The patient's neurologist got wind of the fact that she was thinking about surgery for this problem and he said, "The examination is complicated by a functional overlay." By which, he meant that she could do backwards walking better than forwards walking. He said, "I think it is very unlikely that the disc protrusions are contributing to the autonomic and other symptoms. As such, this would not be a circumstance where I would recommend surgery." So, there is a gap between the neurosurgical and the neurological views.

Anyway, she had her procedure. She noted something was much better within the first week. She had less of that burning in her legs. Her shoulders weren't hunched when she walked. And she was able, even in the first week post-op, to talk a walk for 30 minutes with her mother. She was gradually able to do progressively more.

By the two-month point, she was eating out at restaurants, having really been homebound for most of the last couple of years, walking ten minutes a day. By eight months' post-op, she progressed to 35 minutes a day. Her sensation was improved. In fact, she was helping her parents paint the house. They said to me, "You know, all this is really good and everything; but we need to get her out of here." She was doing so well that she was bothering them.

Her heart rate also changed: before surgery, where she had a huge increase in heart rate with standing; and afterwards, no longer met the criteria for POTS, she had a 25-beat change in heart rate. The initial standing test provoked her symptoms. The post-operative standing test did not.

This is another patient that I had presented, I think, last year at this meeting. This is a girl who had about seven years of POTS and fatigue and some free-floating anxiety, did not have a neurologic examination abnormality until about the seventh year when I recognized the Hoffman sign being abnormal; but it had not been before, at least by my exam. We got an MRI and she had congenital cervical narrowing with a big disc bulge in the lower half of the C-spine. The same surgeon did a disc replacement with her. She went from really being unable to be active with her college education, maybe taking one course every semester, to now, ever since the surgery, able to be a full-time student, active doing wedding photo shoots each weekend, working in a retail store 15 hours a week— really making up for lost time.

Her clivo-axial angle is by no means normal; but by treating the disc protrusion, she had a big improvement in symptoms. You can also now observe a very nice improvement in her hemodynamics response. Her heart rate was getting up to 150 bpm within ten minutes, actually with only five minutes of standing in her case. Afterwards, she had only a 15-beat increase in heart rate when she was standing.

My concluding points would be that we know that syncope may be a presenting feature of Chiari malformation, and that you can get improvement in syncope and other forms of orthostatic intolerance after decompression of the Chiari. And non-syncopal orthostatic intolerance can be an early manifestation of Chiari before the classical signs and symptoms emerge.

However, the last two patients discussed showed that correction of ventral compression of the cord, from either a congenital or acquired cervical stenosis, can be associated with marked functional improvement and improved objective cardiovascular indices.

I think, as we move forward, establishing standing tests or other autonomic measures before and after treatment would be valuable in being able to assess response to treatment.

Thank you.

Discussion following presentation

DR. MARK LUCIANO: Thank you very much. Very, very good talk.

Not to stay fixated on one topic; but is there any information on what happens if you took fluid out of the spinal canal through either a catheter or lumbar puncture; do you get a neuro-adrenergic response or do you get any response in the case of low cranial pressure or CSF leak?

DR. PETER ROWE: I'm not sure. I don't think anyone has done that work.

DR. MARK LUCIANO: Because that could be part of the etiology.

The other thing I noticed is that in the first of the last two cases you showed, the inflow from the aqueduct was below the tentorium and the anterior area; in other words,

it was one of the criteria for sagging brain. Further, those discs, which otherwise look benign, sometimes are the cause of CSF leak.

So I'm just wondering if by fixing the disc, you take away the disc and the leak seals up. This has happened in leaks that were known. And if CSF itself is causing a surge in the neuro-adrenergic system, it could kind of all come together.

DR. ROWE: Yes. I think those are great points. I do not think these patients were worked up in that systematic a way.

DR. ANDREAS LINNINGER: Forgive me, a very distant comment again from hydraulics here. What I think is shown is the change in auto-regulation.

Initially when the heartbeat goes up so much, if I understand it correctly, this may not really indicate that the nerves are not able to control what we are reading, but it just asks the heart to beat hard because there is a lot of resistance.

So I'm just submitting here that in these cases it may not be a function that the nerves are compressed in such a way that they fail to control; but the heart has to beat so hard because of the increased resistance.

And from the work we did in the perfusion of the cerebral cortex, we find that most of the resistance is in the capillary bed. I just want to venture to say that if you had such a situation in the brain of an increase in pressure or compression, causing an increase of flow resistance, then this would mean that the heart has to work so hard against the perfusion pressure. That goes away when you treat the problem.

So in patient who is saying that there is a loss of nervous control or with the systemic circulation, we should maybe also think about the possibility of having an increase in perfusion resistance that may cause these patients to suffer so much; and then when you remove the condition, the flow is not obstructed and it doesn't cause an increase.

DR. ROWE: Yes. And it might dovetail nicely with some data that I did not show here, wherein investigators looked at the response to upright posture: one of the physiologic changes is to take deeper respirations to create a negative intrathoracic pressure to try and suction the blood back up. That works for one or two cycles; but if you continue that, you are going to get cerebral vasoconstriction. So maybe there is an interplay there as well.

DR. ROGER KULA: In the last two cases was there any flexion and extension sagittal imaging to see if there was any dynamic change in the discs or buckling of the posterior ligaments?

DR. ROWE: Yes. I do not have those. I think the surgeon did flexion and extension X-rays, but I do not think they were MRIs.

DR. FRASER HENDERSON: I think those last two cases of the cervical discs underscore the importance of the sympathetic tracts in the spinal cord, so we should be looking for causes of dysautonomia in the cervical spine and even the thoracic spine.

Would you agree?

DR. ROWE: Yes, I would.

[1] Bai Y, Komarow, HD, Lindsley A, Lyons JJ, Milner JD, et al. Mendelian inheritance of elevated serum tryptase associated with atopy and connective tissue abnormalities. J Allergy Clin Immunol. 2015 May; 133(5): 1471-1474.

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[11] Nogués M, Delorme R, Saadia D, Heidel K, Benarroch E. Postural tachycardia syndrome in syringomyelia: response to fludrocortisone and β–blockers. Clinical Autonomic Research. 2001; 11:265-167.

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