Refractory Syncope and Presyncope Associated with Atlantoaxial Instability: Preliminary Evidence of Improvement Following Surgical Stabilization

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■ BACKGROUND: **The proclivity to atlantoaxial instability (AAI) has been widely reported for conditions such as rheumatoid arthritis and Down syndrome. Similarly, we have found a higher than expected incidence of AAI in hereditary connective tissue disorders. We demonstrate a strong association of AAI with manifestations of dysautonomia, in particular syncope and lightheadedness, and make preliminary observations as to the salutary effect of surgical stabilization of the atlantoaxial motion segment.**

■ METHODS: **In an institutional review board–approved retrospective study, 20 subjects (16 women, 4 men) with hereditary connective tissue disorders had AAI diagnosed by computed tomography. Subjects underwent realignment (reduction), stabilization, and fusion of the C1-C2 motion segment. All subjects completed preoperative and postoperative questionnaires in which they were asked about performance, function, and autonomic symptoms, including lightheadedness, presyncope, and syncope.**

■ RESULTS: **All patients with AAI reported lightheadedness, and 15 had refractory syncope or presyncope despite maximal medical management and physical therapy. Postoperatively, subjects reported a statistically significant improvement in lightheadedness ($P = 0.003$), presyncope ($P = 0.006$), and syncope ($P = 0.03$), and in the frequency ($P < 0.05$) of other symptoms related to autonomic function, such as nausea, exercise intolerance, palpitations, tremors, heat intolerance, gastroesophageal reflux, and sleep apnea.**

■ CONCLUSIONS: **This study draws attention to the potential for AAI to present with syncope or presyncope that is refractory to medical management, and for surgical stabilization of AAI to lead to improvement of these and other autonomic symptoms.**

INTRODUCTION

In the last few years, we have recognized a significant relationship between refractory syncope, presyncope, and atlantoaxial instability (AAI). In this study, we demonstrate the association of a statistically significant improvement in syncope, presyncope, lightheadedness, and other autonomic symptoms with surgical stabilization of the atlantoaxial segment. We present a discussion of syncope and other manifestations of autonomic dysfunction, as the casualties of mechanical stress imposed by pathological rotary AAI on the lower brainstem and upper spinal cord.[1-13]

There is an increased prevalence of AAI in persons with hereditary connective tissue disorders (HCTD).[14] It is not surprising that increased ligamentous laxity due to intrinsic defects of the connective tissue may result in pathological subluxation of the

Key words
- Atlantoaxial instability
- Autonomic nervous system
- Ehlers-Danlos syndrome
- Presyncope
- Syncope

Abbreviations and Acronyms
AAI: Atlantoaxial Instability
CT: Computed tomography
EDS: Ehlers-Danlos syndrome
HCTD: Hereditary connective tissue disorder
OGS: Orthostatic Grading Scale

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Table 1. Intake Questionnaire Used to Assess Preoperative and Postoperative Symptoms

Indicate Severity Using Number Scale | 1 = None | 2 = Mild | 3 = Moderate | 4 = Severe | 5 = Incapacitating

Neurological						Musculoskeletal					
Hyperacusis/sensitivity to noise	1	2	3	4	5	Neck pain on bumpy roads	1	2	3	4	5
Ringing in the ears	1	2	3	4	5	Muscle pain at rest	1	2	3	4	5
Loss of hearing	1	2	3	4	5	Cramps/stiff muscles	1	2	3	4	5
Balance disorder	1	2	3	4	5	Pain in legs while walking	1	2	3	4	5
Vertigo (room spinning around)	1	2	3	4	5	Back pain when lying down	1	2	3	4	5
Dizziness/lightheadedness	1	2	3	4	5	Scoliosis	1	2	3	4	5
Shaking episodes (dystonias)	1	2	3	4	5	Back pain walking up incline	1	2	3	4	5
Seizures	1	2	3	4	5	Lower back pain	1	2	3	4	5
Tremors	1	2	3	4	5	Sacral pain	1	2	3	4	5
Headache	1	2	3	4	5	Sleep with knees bent	1	2	3	4	5
Neck pain	1	2	3	4	5	Cardiovascular/autonomic nervous system					
Loss of consciousness/syncope	1	2	3	4	5	Feeling heart beats/palpitations	1	2	3	4	5
Presyncope	1	2	3	4	5	Chest tightness/pain at rest	1	2	3	4	5
Concentration difficulties	1	2	3	4	5	Chest pain on exertion	1	2	3	4	5
Memory loss	1	2	3	4	5	Shortness of breath at night	1	2	3	4	5
Blurred vision	1	2	3	4	5	Shortness of breath at rest	1	2	3	4	5
Double vision	1	2	3	4	5	Shortness of breath on exertion	1	2	3	4	5
Teichopsia (vision flashes)	1	2	3	4	5	Fingers change color with temperature	1	2	3	4	5
Photosensitivity (light sensitivity)	1	2	3	4	5	Excessive sweating	1	2	3	4	5
Hyperolfaction (sensitivity to smell)	1	2	3	4	5	Heat intolerance	1	2	3	4	5
Facial numbness	1	2	3	4	5	Elevated temperature of >101.5°	1	2	3	4	5
Paresthesia/tingling/sensory loss	1	2	3	4	5	Sleep disturbances	1	2	3	4	5
Leg weakness	1	2	3	4	5	Abnormally dilated pupils	1	2	3	4	5
Arm weakness	1	2	3	4	5	Gastrointestinal					
Nausea/vomiting	1	2	3	4	5	Abdominal pain	1	2	3	4	5
Poor coordination	1	2	3	4	5	Bloating	1	2	3	4	5
Speech difficulty	1	2	3	4	5	Constipation	1	2	3	4	5
Hoarseness	1	2	3	4	5	Heart burn/GERD	1	2	3	4	5
Choking	1	2	3	4	5	Diarrhea	1	2	3	4	5
Difficulty swallowing	1	2	3	4	5	Black stool/blood in stool	1	2	3	4	5
Constitutional						Loss of bowel control	1	2	3	4	5
Fatigue	1	2	3	4	5	Genitourinary					
Rashes	1	2	3	4	5	Burning with urination (dysuria)	1	2	3	4	5
Easily bruised	1	2	3	4	5	Increased frequency/urination	1	2	3	4	5
Joint pain	1	2	3	4	5	Loss of bladder control	1	2	3	4	5
Poor wound healing	1	2	3	4	5	Nocturia (urination at night)	1	2	3	4	5
Frequent infections	1	2	3	4	5	Difficulty initiating stream	1	2	3	4	5
Anemia	1	2	3	4	5	Unable to empty bladder	1	2	3	4	5
Excessive bleeding	1	2	3	4	5	Enuresis (bedwetting)	1	2	3	4	5

GERD, gastroesophageal reflux disease.

Continues

Table 1. Continued

Indicate Severity Using Number Scale | 1 = None | 2 = Mild | 3 = Moderate | 4 = Severe | 5 = Incapacitating											
Swollen lymph nodes	1	2	3	4	5	Psychiatric					
Thyroid disorder	1	2	3	4	5	Depression	1	2	3	4	5
						Anxiety/panic	1	2	3	4	5

GERD, gastroesophageal reflux disease.

facets at the C1-C2 motion segment,[15] given that the atlantoaxial joint (C1-C2) is the most mobile joint, held together by ligaments that allow freedom of rotation, flexion, and extension.[16-19] AAI is common in many disorders of connective tissue, such as Down syndrome,[20-22] Ehlers-Danlos syndrome (EDS),[18,19] Goldenhar syndrome,[23] and rheumatoid arthritis.[1,2,12] Connective tissue disorders are not primarily a Caucasian phenomenon; epidemiological studies suggest that hypermobility is more prevalent in African and Asian groups than in the white populations.[24]

Rotary AAI is due primarily to alar ligament incompetence and results in pathological angulation of C1 on C2,[14] decreased canal diameter,[25] risk of spinal cord compression and adverse mechanical tension on the spinal cord and lower brainstem,[2,25] and obstruction of cerebrospinal fluid flow, the effects of which precipitate headache and neurological deficits[6,26-30] and kinking of the vertebral arteries with possible intermittent ischemia.[31]

The HCTD population is known to have an increased prevalence of autonomic symptoms and orthostatic intolerance.[32-35] We have reported elsewhere on the diagnosis, surgical technique, and neurological outcomes of this cohort.[36] This paper addresses the prevalence of syncope, presyncope, and orthostatic intolerance in this cohort, and emphasizes the potential for improvement in autonomic symptoms after atlantoaxial stabilization surgery.

MATERIALS AND METHODS

The details of participant inclusion criteria, radiological methods for diagnosis, operative techniques, and general outcomes have been reported elsewhere.[36]

Subject Enrollment

Over a 2-year period (2016–2018), 23 consecutive subjects diagnosed with rotary underwent C1-C2 reduction, fusion, and stabilization. Twenty individuals completed follow-up questionnaires and comprise this cohort.

Evaluation

At their initial assessment visits, patients completed a routine clinical intake questionnaire that recorded the presence or absence of specific symptoms of lightheadedness (Table 1). The preoperative frequency of syncope and presyncope was extracted from the neurosurgeons clinical notes and intake questionnaire. Participants were contacted 12–24 months after surgery and asked to recall the frequency of lightheadedness, presyncope, and syncope in the month before surgery and in the month before questionnaire completion postoperatively. The frequency of symptoms was reported using a 5-point scale (never, 1–3 times/month, weekly, multiple times weekly, and daily), and these were corroborated with the initial history and clinic notes, which included discussion of syncope and presyncope.

All participants completed the Orthostatic Grading Scale (OGS), a 5-item scale that asks about the frequency and severity of orthostatic symptoms, conditions under which orthostatic symptoms occur, interference with activities of daily living, and the duration of standing time before experiencing orthostatic symptoms. Items were scored from 0 (no or minimal orthostatic symptoms) to 4 (maximal frequency/severity impact of orthostatic symptoms).

As previously reported, neurological examinations were performed by the neurosurgeons (FCH and RR), and radiological measurements by the neuroradiologist (MK).[36] Subjects underwent preoperative computed tomography (CT) of the cervical spine, with the neck maximally rotated (usually 75°–90°) to the left and to the right. On full rotation, the angle subtended by C1 and C2 was measured. An angle greater than 41° represented atlantoaxial rotary subluxation (Fielding Type 1); when 3D-CT reconstruction was available, C1-C2 facet subluxation was assessed (Figure 1). When lateral rotation of the neck was not possible due to pain or neurological symptoms, digital dynamic fluoroscopy was also used to measure pathological translation between C1 and C2 on lateral tilting.[37] Lateral translation of C1 on C2 exceeding 3.5 mm was considered pathological. Postoperative CT was performed at 3–16 months to assess fusion.

Inclusion Criteria for C1-C2 Fusion Surgery

All subjects met the following criteria:

- Formal genetics evaluation and diagnosis with an HCTD (CF).
- Severe headache and/or neck pain for more than 6 months.
- Symptoms compatible with AAI.[13,38,39]
- Congruent neurological deficits.
- Radiological findings—an angle at the extreme of lateral rotation between C1-C2 greater than 41° and/or C1-C2 facet overlap of less than 10% (Figure 1).[35,40] In some cases, radiological findings were augmented by x-ray demonstration of lateral movement (translation) of >3.5 mm on open mouth views.[37,41,42]
- Failed conservative treatment, including a reasonable trial of physical therapy (including isometric exercises of the neck), activity modification, pain medications, neck brace, and other modalities.

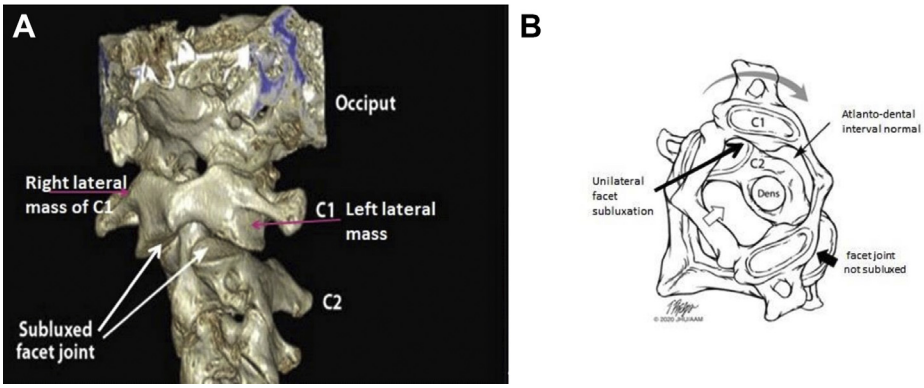

Figure 1. (**A**) Computed tomography 3D reconstruction of the craniocervical junction on full neck turning to the left, showing over 90% loss of facet overlap on the left, with near dislocation of both facet joints. (**B**) Illustration of the Fielding Type 1 rotary subluxation, on full neck rotation to the right (*curved gray arrow*), with near dislocation of the left facet joint (*large black arrow*). The C1 ring lies above the C2 vertebra. The upper facet (left), labeled C1, overlies and has minimal coverage of the underlying superior facet of C2, labeled C2. The atlantodental interval (*small thin black arrow*) remains in the normal range (<3 mm). The contralateral facet joint (*short black arrow*), ipsilateral to the direction of rotation, is not fully subluxed. The subluxation results in marked diminution of the spinal canal diameter (*short white arrow*), which reduces or eliminates cerebrospinal fluid flow and potentially causes spinal cord compression.

Operative Technique

The surgical technique used for these patients is described in detail elsewhere.[36] Briefly, we use a modified technique of Goel and Harms.[43-45] The fusion was performed with an iliac crest allograft, infused with autologous bone marrow (Figure 2). Patients wore a neck brace for 1 month after surgery and then began physical therapy for posture and isometric muscle strengthening exercises.

Statement of Human and Animal Rights

Clinical data were collected and analyzed in accordance with the ethical standards of the institutional review board at Greater Baltimore Medical Center.

Statistical Analysis

For comparisons of pre- and postoperative data for each participant, we used paired t-tests for normally distributed data and the Wilcoxon paired rank test for paired ordinal data or for continuous variables that were not normally distributed. Statistical analyses were conducted using IBM Statistics SPSS55 version 25 (IBM Statistics, New York, USA), and illustrations were prepared using GraphPad Prism version 8.3.0 for Windows (GraphPad Software, La Jolla, California, USA, www.graphpad.com).

RESULTS

The cohort comprised 4 males and 16 females with a mean age 34 years (range, 18–54 years). Nineteen were diagnosed with EDS, and 1 was diagnosed with hypermobility spectrum disorder. The median interval between surgery and completion of the follow-up questionnaires was 20 months (range, 12–44 months).

Preoperative Clinical Findings

As discussed in detail previously,[36] the patients characteristically reported frequent syncopal or presyncopal episodes on a daily or weekly basis and visual changes, including teichopsia, decreased peripheral or tunnel vision with poor spatial awareness, "a

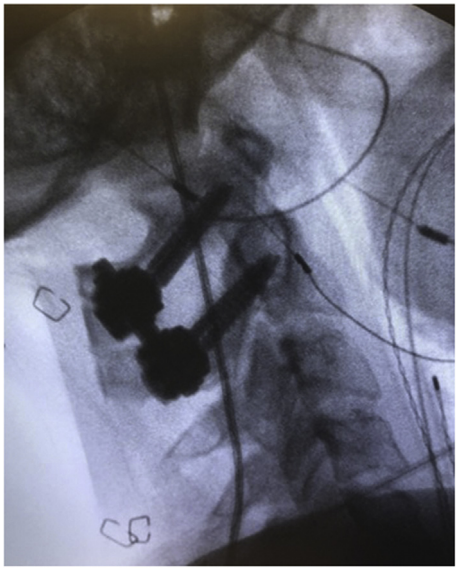

Figure 2. Intraoperative x-ray of the upper cervical spine (sagittal view) showing screw/rod stabilization of C1-C2, with the bone graft lying between the ring of C1 above and the spinous process of C2 below.

brownout" or extreme blurring of vision. They also reported poor concentration and memory, nausea, tinnitus, and intermittent dysesthesias of the extremities.

Three physical findings were remarkably consistent: hyperreflexia (except in those patients with B12 deficiency); hypoesthesia to pinprick over the cervical, thoracic, lumbar, and sacral dermatomes (subjects reported sharpness, but no pain); and tenderness over the C1-C2 motion segment.

Orthostatic Symptoms and Syncope

The preoperative intake symptom form confirmed that all 20 subjects reported orthostatic lightheadedness. Abstraction of the clinical notes identified 10 individuals with at least 1 episode of syncope, 8 of whom had experienced multiple episodes of syncope, including 3 who had weekly episodes. Presyncope was reported by an additional 5 individuals, at frequencies ranging from weekly to 4 times daily. Preoperative symptom frequency compared with postoperative symptom frequency at the time of questionnaire completion is displayed in Table 2.

Postoperatively, patients reported statistically significant improvements in the frequency of lightheadedness, presyncope, and syncope. Given that syncope can be aborted by sitting or lying down, we also examined the combined category of the worst frequency for either syncope or presyncope. In all, 4 of the subjects reporting syncope preoperatively no longer reported syncope in the postoperative period, one of whom had been experiencing weekly episodes. Of those with either syncope or presyncope preoperatively, 8 of 19 subjects had resolution of this symptom (Figure 3). Lightheadedness was also significantly decreased in terms of frequency and the quantity of time that a patient could stand without experiencing symptoms of lightheadedness increased (Figure 4).

OGS Results

The OGS scores were all numerically lower postoperatively (Table 3). The difference was statistically significant for the conditions under which orthostatic symptoms occur. This item asks whether and to what degree subjects experience "orthostatic symptoms under certain conditions, such as prolonged standing, exertion (e.g., walking), or when exposed to heat (e.g., hot day, hot bath, hot shower)." Preoperatively, the median score was 3, representing that they *usually* experienced orthostatic symptoms under those conditions, and postoperatively, the score was 2, representing *often* experiencing those symptoms. The combined score of all 5 OGS items also reflected a significant improvement postoperatively.

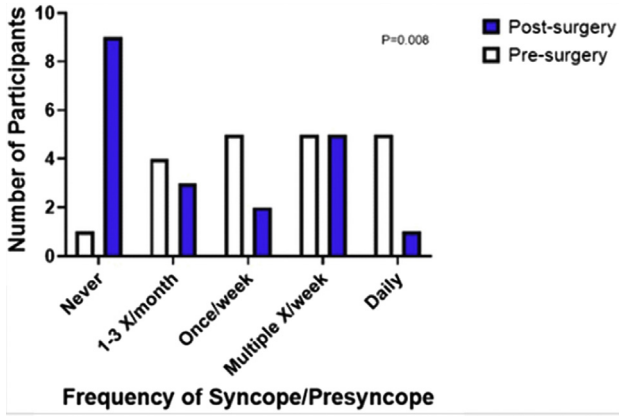

Figure 3. Preoperative syncope frequency (*white columns*) compared with postoperative frequency (*blue columns*) shows a statistically significant decrease in the frequency of presyncope and syncope.

Other Findings Related to Autonomic Function

Patients demonstrated a statistically significant improvement in the frequency and severity of nausea, exercise intolerance, and anxiety. Significant improvement was limited to frequency of symptoms, but not severity, of heat intolerance, gastroesophageal reflux disease, and palpitations (Table 4).

Exercise Intolerance

After atlantoaxial stabilization there was a statistically significant improvement in both intensity and frequency of exercise intolerance (Figure 5).

Table 2. Orthostatic Symptom Changes After Surgery

Symptom	Frequency	Never	1–3/month	1/week	Multiple Times/week	Daily	*P**
Lightheadedness	Preoperative	0	0	5	4	11	
	Postoperative	0	3	10	4	3	0.003
Syncope	Preoperative	11	2	2	2	3	
	Postoperative	15	3	0	2	0	0.03
Presyncope	Preoperative	2	3	6	4	5	
	Postoperative	9	3	3	4	1	0.006
Presyncope/syncope*	Preoperative	1	4	5	5	5	
	Postoperative	9	3	2	5	1	0.008

*Wilcoxon signed ranks test for paired data.

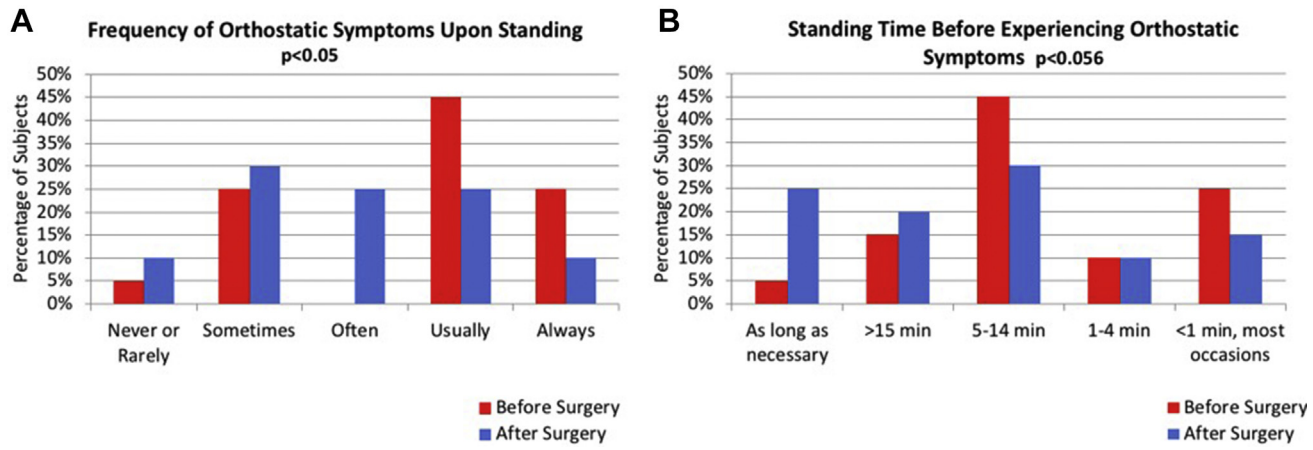

Figure 4. (**A**) Frequency of subjects' orthostatic symptoms on standing. (**B**) Length time before subjects experienced orthostatic changes while standing.

DISCUSSION

This study draws attention to the potential for AAI to present with various forms of disordered autonomic function (dysautonomia), in particular, syncope or presyncope. The study also suggests that surgical stabilization of AAI leads to improvement of these symptoms. We believe that this is the first study to examine the hypothesis that AAI deleteriously affects the autonomic nervous system, and that correction of AAI manifests in improvement of autonomic symptoms.

This was clear from the resolution of syncope in 4 of 9 patients, and in the statistically significant improvements in the frequency of lightheadedness and presyncope in others. We emphasize that the individuals in this cohort had been refractory to medical management of their orthostatic intolerance and had persistence of these symptoms despite physical therapy, along with other characteristic symptoms and examination features of AAI.

Syncope and Presyncope Improved Postoperatively

Our results extend previous observations that syncope can be a presenting feature of Chiari malformation, syringomyelia, and cervical spinal stenosis.[46-48] At a minimum, the results from this cohort should alert clinicians to the possibility that refractory syncope and presyncope can be causally related to AAI. These observations will need to be replicated in a study with prospective collection of symptom data.

Syncope or episodic loss of consciousness in the context of Chiari malformation has been variously attributed to raised intracranial pressure, to mechanical obstruction of the vertebrobasilar arteries, compression of the brainstem itself, or "percussion of the brainstem against the clivus."[7,49] Sudden appearance of low amplitude slowing of the electroencephalogram heralding the onset of loss of consciousness has been attributed to "midbrain concussion" from compression and shearing forces, with dysfunction of the ascending reticular activating system. Syncope, occipital headache, double vision, and numbness in patients with syringomyelia have been attributed to autonomic disturbance of the sympathetic system in the lower brainstem.[48,50]

Autonomic symptoms occur with regularity in EDS and other HCTD.[32,51,52] We propose 2 potential explanations for what was

Table 3. Orthostatic Grading Scale Scores

Median	Preoperative	Postoperative	*P* Value
Frequency of orthostatic symptoms	3	2	0.06
Severity of orthostatic symptoms	2	2	0.10
Conditions under which orthostatic symptoms occur	3	2	0.04
Activities of daily living	2	1	0.11
Standing time	2	2	0.08
Combined Orthostatic Grading Scale score	12.0	7.5	0.04

Table 4. Other Findings Related to Autonomic Function

Symptom/ Problem	% Pre Surgery	% Post Surgery	% With Improvement in Frequency Post Surgery*	% With Worsening of Frequency Post Surgery*	*P* Value for Frequency	% With Onset Post Surgery	% With Improvement Severity Post Surgery*	% With Worsening of Severity Post Surgery*	*P* Value for Severity
Nausea	90% (18/20)	75% (15/20)	61.1% (11/18)	11.1% (2/18)	***<0.021***	0	44.4% (8/18)	16.7% (3/18)	***<0.045***
Heat intolerance	85% (17/20)	85% (17/20)	41.2% (7/17)	5.9% (1/17)	***<0.036***	0	35.3% (6/17)	11.8% (2/17)	<0.3
GERD	50% (10/20)	50% (10/20)	40% (4/10)	0	***<0.043***	0	10% (1/10)	10% (1/10)	1
Dizziness	100%	100%	60% (12/20)	15% (3/20)	***<0.018***	0	50% (10/20)	15% (3/20)	*<0.057*
Anxiety	90% (18/20)	85% (17/20)	55.6% (10/18)	11.1% (2/18)	***<0.023***	0	44.4% (8/18)	11.1% (2/18)	***<0.029***
Exercise intolerance	85% (17/20)	80% (16/20)	52.9% (9/17)	5.9% (1/17)	***<0.039***	0	64.7% (11/17)	11.8% (2/17)	***<0.007***
Sleep apnea/ night awakening	85% (17/20)	75% (15/20)	23.6% (4/17)	0	*<0.07*	0	41.2% (7/17)	5.9% (1/17)	***<0.029***
Palpitations	80% (16/20)	75% (15/20)	37.5% (6/16)	6.3% (1/16)	***<0.038***	0	43.8% (7/16)	12.5% (2/16)	*<0.07*

GERD, gastroesophageal reflux disease.
All the bolded/italicized values reflect $P < 0.05$, or statistical significance.
Non-bolded values are $P > 0.05$.
*For those participants who had the presence of a symptom/problem before surgery (note: most symptoms are multifactorial).

predominantly sympathetic autonomic dysfunction. Drawing on concepts first elaborated by Breig, the authors suggest that low-grade chronic mechanical stretching and deformity of neural tissue in the ventrolateral medulla[53] and upper spinal cord result in transient or permanent neurological injury.[4,5,54-56] Torsion of the upper spinal cord should be seen in the context of localized attachment of the cord by the denticulate ligaments, which secure the cord to the dura and act as the *agents of limitation* (Figure 6A).

The torsional strain is most severe where the rotation is greatest in the segment between the fixed brainstem and the spinal cord at C1and C2 (Figure 6B).[4,57] Moreover, the stress is profoundly increased by intermittent compression of the spinal cord.[4]

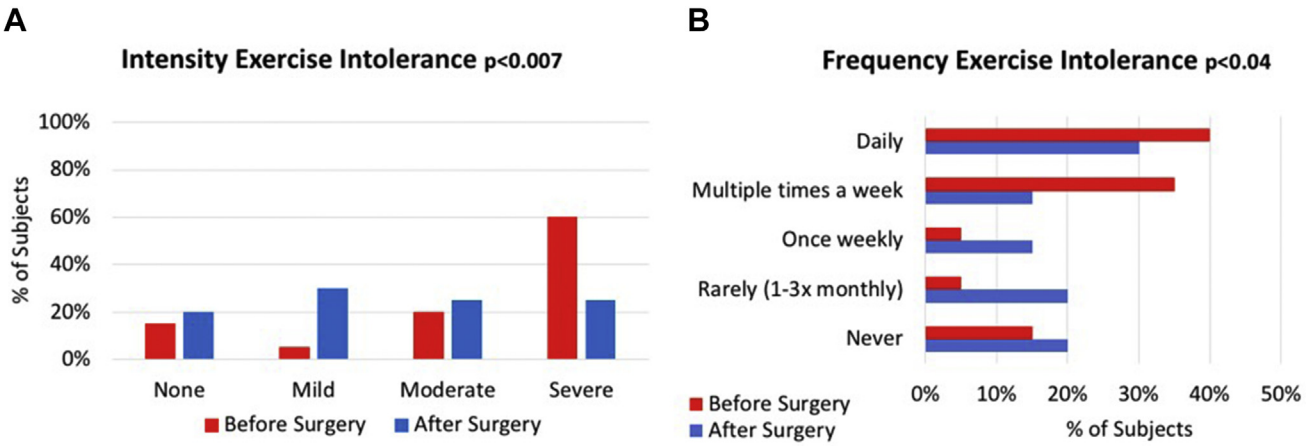

Figure 5. (**A**) Intensity of exercise intolerance before and after atlantoaxial stabilization. (**B**) Frequency of exercise intolerance before and after atlantoaxial stabilization.

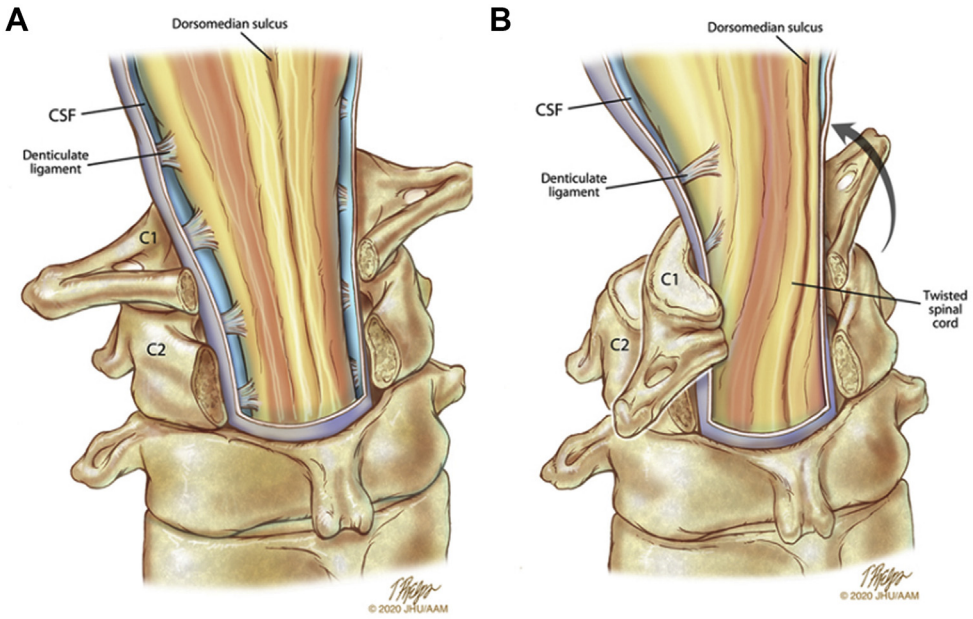

Figure 6. (**A**) Illustration from the posterior view of the lower brainstem and upper spinal cord in the neutral (unrotated) state. Note that the denticulate ligaments attach to—and suspend—the spinal cord within the dura bilaterally. Cerebrospinal fluid (CSF; indicated in blue) flows circumferentially around the cord to and from the intracranial compartment to the spinal compartment. (**B**) In the case of neck rotation with an atlantoaxial subluxation (*gray arrow* showing the direction of rotation to the subject's left), there is mechanical torsion of the spinal cord between the denticulate ligaments at the C1 and C2 levels. With rotation, there is occlusion of the spinal canal with consequent loss of CSF space, obstruction of CSF flow, and possible compression of the spinal cord.

Spinal canal stenosis (diameter of canal 1 cm) was found in 39% of normal subjects on full neck rotation. Thus, in rotary AAI, the accentuated narrowing of the canal may be expected to add some degree of compression to the spinal cord.[25] The "out of plane loading" from this compression geometrically increases the *Von Mises stress* within the neuraxis under torsion.[4,57]

Excessive rotation of C1 on C2 may obstruct blood flow through the vertebral arteries.[26] In the setting of AAI, head rotation causes the atlas on the side opposite the direction of rotation to move forward and downward, thus kinking the contralateral vertebral artery, with a consequent decrease or even complete obstruction of flow (**Figure 6**).[26,31] Vertebral artery flow may further be diminished by occipital or craniocervical junction anomaly, hypertrophy of the atlanto-occipital membrane, tightness of the paravertebral muscles, and constriction by fibrous bands.[31]

AAI May Dysregulate the Cardiovascular System

The pathophysiology of syncope is multifactorial, resulting from decreased cardiac output, decreased vasoconstriction, or activation of the cardioinhibitory vasodepressor reflex. Cardiac output is regulated through stretch-sensitive baroreceptors of the aortic arch and the carotid arteries, which maintain tonic activity in a split-second negative feedback loop through the vagal and glossopharyngeal nerves, respectively.[58] The inotropic effects of the sympathetic nervous system are normally counterbalanced by cholinergic, parasympathetic, preganglionic neurons exerted through the vagus nerve. Imbalance of autonomic influence may arise in the setting of low-grade chronic injury to the descending central sympathetic autonomic fibers within the spinal cord.[8] The vagus nerve exits the upper level of the medulla, is not subject to the pathological deformative stresses incurred in rotary AAI, and may therefore assume a dominant, unbalanced influence over cardiovascular function. This is another example of brain stem injury among a list of structural pathologies causing autonomic dysfunction.[59]

There are many levels of the central nervous system in which dysregulation could occur. Baroreceptors are mechanoreceptors that use a viscoelastic coupling to alter rate sensitivity, adaptation, and hysteresis. This viscoelastic coupling may be altered in hereditary disorders of connective tissue and result in inadequate or exaggerated response to blood pressure changes.

Headache Is Mediated by Both Somatic and Sympathetic Nerves

AAI in this population was most commonly characterized by severe headaches. Headache in the distribution of the occipital nerves has been attributed to mechanical stresses on the C2 dorsal roots. Unlike all other spinal nerves that exit through the neural foramina, the C2 roots exit unprotected between the laminae.

A second mechanism of occipital pain may be mediated by sympathetic nerves investing the dura and accompanying the

vertebral arteries. The vertebral nerve, comprising fibers from the middle and superior sympathetic ganglia,[60,61] is vulnerable to trauma and is thought to be the anatomic substrate for the characteristic severe, sudden, localized pain of vertebral artery injury at the C1-C2 level,[62] as well as distributing branches to radicular arteries and veins of the spinal cord.[61,63,64] Pathological tension of the dura and injury to the vertebral artery may cause sympathetically mediated pain.[65,66] Sympathetic fibers, not associated with blood vessels, arise from the stellate ganglia and innervate the dura and posterior longitudinal ligament of the upper cervical spine,[67] whereas those arising from the superior cervical ganglion innervate the dura of the craniocervical region.[68] These sympathetic nerves, distinguished by their lack of close proximity to blood vessels,[67,69] demonstrate neuropeptide Y-immunoreactivity and may influence mast cell activity.

Vision Changes and Poor Spatial Awareness May Be the Result of Posterior Circulation Abnormalities. The majority of subjects in this cohort experienced decreased peripheral vision, manifest in their *poor spatial awareness* and tendency to walk into objects in the periphery of their vision. One patient reported having memorized the location of every object in her room to avoid collision. The authors believe that intermittent compromise of the vertebrobasilar circulation during head rotation may contribute to visual field changes (**Figure 7**).[26,31,70-72] The peripheral visual field lies in the domain of the posterior cerebral arterial circulation, whereas the occipital pole, in which the central or macular vision is represented, derives its blood supply from the middle cerebral artery.[73]

Tinnitus and Vertigo. Intermittent ischemia of the peripheral labyrinth from altered vertebra-basilar flow may also explain tinnitus and nausea.[31,74]

Autonomic Aspects of Behavior. C1-C2 stabilization may exert a salutary effect on the upward synaptic transmission from brainstem to hypothalamus, amygdala, and medial forebrain, temporal and limbic lobes. Activation of C1 neurons is 1 component of the global sympathoexcitation evoked by physiological stressors.[75] The ascending influence on the nucleus coeruleus may reasonably "exert widespread excitatory effects on sympathetic outflow" to the hypothalamus and amygdala.[30,75-77] The authors suspect that impairment of this activation has a deleterious effect on attention and memory.

The Radiological Diagnosis of AAI in the HCTD Population Requires a Directed Investigation and Dynamic Imaging

Anterior subluxation requires flexion and extension images to demonstrate incompetence of the transverse ligament. Lateral subluxation and rotary subluxation require coronal views on lateral tilt or rotational views to demonstrate the alar ligament incompetence.

Fielding and Hawkins[42] described the Type 1 rotatory subluxation as having facet subluxation with a *normal atlantodental interval* (**Figure 1B**). When the angle subtended by the rotation of C1 on C2 is 40°, there is complete obstruction of vertebral blood flow contralaterally. The authors have adopted an angular displacement of ≥41° as the pathological threshold.[35,36,41,42,78]

In this population, AAI is often undiagnosed for several reasons.[36] Rotary subluxation (Fielding Type 1) requires full neck

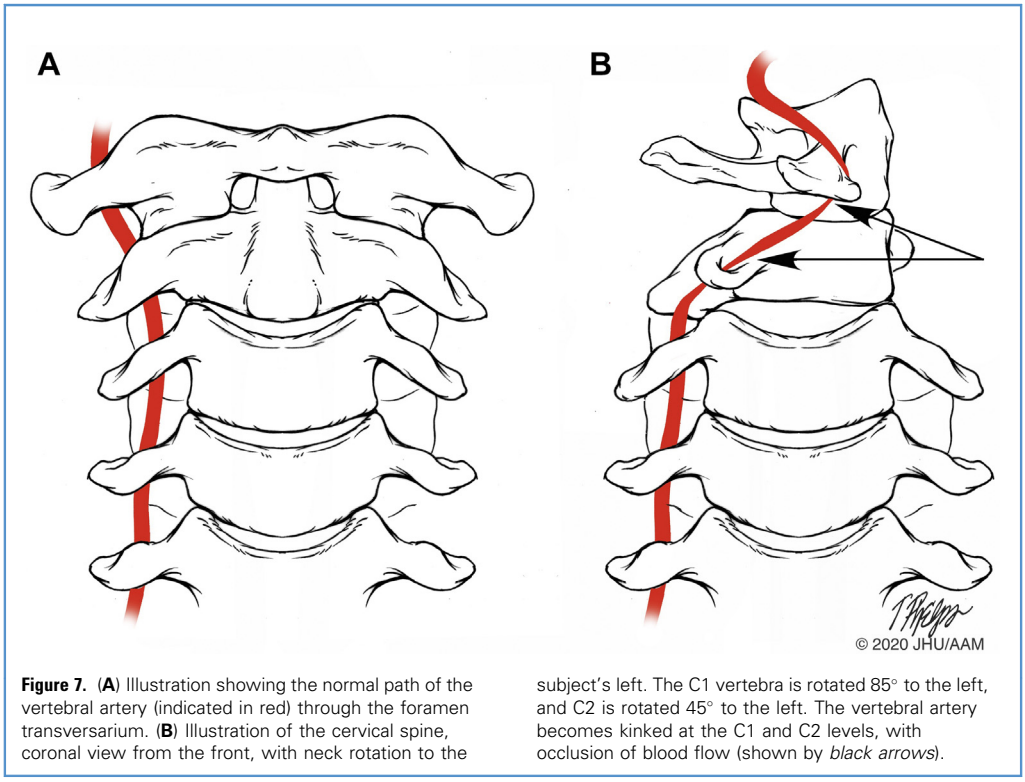

Figure 7. (**A**) Illustration showing the normal path of the vertebral artery (indicated in red) through the foramen transversarium. (**B**) Illustration of the cervical spine, coronal view from the front, with neck rotation to the subject's left. The C1 vertebra is rotated 85° to the left, and C2 is rotated 45° to the left. The vertebral artery becomes kinked at the C1 and C2 levels, with occlusion of blood flow (shown by *black arrows*).

rotation (80°—90°) to demonstrate alar ligament incompetence. However, dynamic CT with neck rotation is not a standard technique. Technicians, moreover, are often reluctant to encourage the patient to fully rotate the neck. Those in whom pain prevents sufficient neck rotation may require dynamic lateral neck tilting (open mouth view) to assess lateral translation of C1 on C2. Translational displacement greater than 3.5 mm is considered pathological.[36-57,67-79]

Limitations

This study was a retrospective examination of a relatively small cohort of 20 surgical subjects. Three subjects (of 23 total subjects to whom questionnaires were sent) did not return questionnaires; we cannot exclude the possibility that they had less positive outcomes. A larger study may have improved the power of the study to identify other areas of symptomatic improvement. There was no control for placebo effect. Although an independent nurse collected the data, subjects might have responded to questionnaires in the direction they perceived the investigators desired (*obsequiousness bias*). We cannot exclude patient recall bias. Comorbid conditions profoundly impacted the majority of subjects and may have negatively influenced the outcome metrics. We cannot completely exclude the possibility that there was a spontaneous, coincidental improvement in orthostatic symptoms after surgery, although this seems unlikely.

CONCLUSION

A syndrome of severe headache, syncope or presyncope, visual symptoms, and dysautonomia should prompt consideration of AAI in persons with hereditary disorders of connective tissue. The diagnosis of rotary AAI requires directed investigation, including *dynamic* imaging. Dysfunction of the autonomic nervous system, dysautonomia, was universally present in this cohort. Frequency and severity of syncope and presyncope were substantially improved by C1-C2 stabilization. The autonomic nervous system appears to be adversely affected by instability at the craniocervical junction and improved by correction of instability.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Fraser C. Henderson: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Supervision, Project administration, Funding acquisition. **Peter C. Rowe:** Conceptualization, Methodology, Software, Validation, Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **Malini Narayanan:** Validation, Data curation. **Robert Rosenbaum:** Methodology, Investigation. **Myles Koby:** Methodology, Formal analysis, Investigation. **Kelly Tuchmann:** Data curation, Formal analysis. **Clair A. Francomano:** Conceptualization, Validation, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Funding acquisition.

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