

Neurosurgical management of patients with Ehlers–Danlos syndrome: A descriptive case series

ABSTRACT

Introduction: Ehlers–Danlos syndrome (EDS) is a connective tissue disorder that has been linked to several neurological problems including Chiari malformations, atlantoaxial instability (AAI), craniocervical instability (CCI), and tethered cord syndrome. However, neurosurgical management strategies for this unique population have not been well-explored to date. The purpose of this study is to explore cases of EDS patients who required neurosurgical intervention to better characterize the neurological conditions they face and to better understand how neurosurgeons should approach the management of these patients.

Methods: A retrospective review was done on all patients with a diagnosis of EDS who underwent a neurosurgical operation with the senior author (FAS) between January 2014 and December 2020. Demographic, clinical, operative, and outcome data were collected, with additional radiographic data collected on patients chosen as case illustrations.

Results: Sixty-seven patients were identified who met the criteria for this study. The patients experienced a wide array of preoperative diagnoses, with Chiari malformation, AAI, CCI, and tethered cord syndrome representing the majority. The patients underwent a heterogeneous group of operations with the majority including a combination of the following procedures— suboccipital craniectomy, occipitocervical fusion, cervical fusion, odontoidectomy, and tethered cord release. The vast majority of patients experienced subjective symptomatic relief from their series of procedures.

Conclusions: EDS patients are prone to instability, especially in the occipital-cervical region, which may predispose these patients to require a higher rate of revision procedures and may require modifications in neurosurgical management that should be further explored.

Keywords: Atlantoaxial Instability, Chiari malformation, craniocervical instability, Ehlers–Danlos syndrome, occipitocervical fusion, suboccipital craniectomy, tethered cord syndrome

INTRODUCTION

Ehlers–Danlos syndrome (EDS) is a heterogeneous group of connective tissue disorders resulting in joint hypermobility and tissue fragility. Several neurological conditions have been linked to EDS, including multiple disorders that may require neurosurgical intervention such as Chiari 1 malformation (CM 1), atlantoaxial instability (AAI), craniocervical instability (CCI), tethered cord syndrome, and more.^[1] In a 2017 review, Henderson *et al.* describe the evidence that CM 1 is a comorbidity of EDS, craniocervical ligament weakness results in CCI and AAI, and how the relationship between EDS and tethered cords has been seen anecdotally.^[1]

Recent advances in the literature have begun to further explore the relationship between connective tissue diseases broadly

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Submitted: 05-Oct-22


Accepted: 25-Dec-22

Published: 13-Mar-23

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How to cite this article: Rock MB, Zhao DY, Felbaum DR, Sandhu FA. Neurosurgical management of patients with Ehlers–Danlos syndrome: A descriptive case series. J Craniovert Jun Spine 2023;14:24-34.

Access this article online	
Website: www.jcvjs.com	Quick Response Code 
DOI: 10.4103/jcvjs.jcvjs_127_22	

or EDS specifically with neurological ailments. Literature has emerged suggesting hypermobility in EDS results in abnormal spinal cord mechanics at the craniocervical junction.^[2] Further studies have helped solidify the connection between CCI and Chiari malformations with EDS, while others have suggested that EDS can disease the filum terminale, increasing the risk of tethered cord syndrome.^[3–5] However, there has been a relative paucity of literature exploring the methods of neurosurgical management for this unique patient population. Given their hypermobility and the fragility of their tissues, it stands to reason that neurosurgical management strategies and outcomes may well differ for this group of patients. In a previous study conducted by the authors of this manuscript, we identified a set of patients that developed CCI after Chiari decompression and went on to be treated with occipitocervical fusion (OCF). Twelve of the fifteen patients, or 80% of the patients in that study, were found to have a history of EDS, suggesting a risk factor for developing CCI after Chiari decompression.^[6] That study not only suggested that EDS predisposes to certain types of instability, but went on to suggest that OCF is a safe and effective treatment option for this patient population. This itself highlights how the EDS patient population may require additional or modified neurosurgical treatment plans compared to other patient groups.

The purpose of this study is to descriptively analyze a retrospective series of patients with EDS who presented with neurological ailments requiring neurosurgical intervention. From this narrative analysis, we aim to better understand the unique neurological problems facing patients with EDS and better characterize methods of successful neurosurgical intervention for this cohort.

METHODS

We retrospectively reviewed clinical records from the electronic health record from January 2014 to December 2020. We identified patients who underwent a neurosurgical operation with the senior author (FAS) during that timeframe and had a concomitant diagnosis of EDS. The patients included all had previously been diagnosed with EDS by another physician before undergoing a neurosurgical procedure with our senior author. These diagnoses were patient-reported or dictated in the electronic health record. These diagnoses were the result of clinical and/or genetic testing. A Beighton score was utilized as a clinical tool to confirm joint hypermobility consistent with EDS in these patients. We excluded any patients who were under the age of 18 years at the time of surgery due to the unique anatomy of pediatric patients, which would have introduced another

element of heterogeneity to this study. We also excluded any patients who initially presented for trauma, tumor, or infection. After identifying our patient cohort, we analyzed their records and documented the following: demographic characteristics, all neurosurgical procedures these patients underwent with the senior author, presenting symptoms, indications for surgery, postoperative complications, clinical outcomes, any additional or past neurosurgical operations, and length of follow-up. We chose five representative case illustrations and collected additional information on their clinical course along with available pre- and post-operative radiographic imaging.

In collecting these data, we had to define parameters in diagnosing the common neurological ailments encountered. Chiari malformations were defined in the standard protocol as radiographic evidence of 5 mm or greater cerebellar tonsillar herniation through the foramen magnum.^[7] AAI is characterized by anterior displacement of the facet primarily on one side with a normal atlantodental interval, which is due to alar ligament incompetence. Radiographic evidence of AAI consists of C1/C2 angular displacement $>41^\circ$ on rotational imaging or C1/C2 facet overlap $<10\%$.^[8] We utilized the angular displacement in our diagnosis of AAI. CCI results in cranial settling with clivo-axial kyphosis and possible ventral brainstem compression as a result of ligamentous laxity and hypermobility. Clivo-axial angle (CXA), Grabb–Mapstone–Oakes measurement, and/or Horizontal Harris measurement can be utilized to support a diagnosis of CCI.^[9] We utilized CXA in supporting the diagnosis of CCI in our patients. Tethered cord syndrome can present with back and/or leg pain, lower extremity sensorimotor deficits, and bladder or bowel dysfunction. The clinical presentation along with urodynamic testing and possibly radiographic evidence of a low-lying conus medullaris can support the diagnosis of tethered cord syndrome.^[5] The senior author utilized clinical presentation along with these radiographic parameters and radiology reports in defining the diagnoses of the patients in this study.

We analyzed records through March 2022 in assessing follow-up, additional procedures, and clinical outcomes. Based on available follow-up information and excluding 3 patients lost to follow-up, we broadly categorized patients into one of three clinical outcome categories: Significant improvement of symptoms, continuation of symptoms, and temporary or mild improvement of symptoms. Significant improvement of symptoms was defined as patients who reported postoperative improvement of symptoms sustained at the most recent follow-up as expressed by a reduction in subjective pain score, potentially alongside a reduction

in other preoperative symptoms, resulting in significantly improved function. Continuation of symptoms was defined as a lack of significant improvement of preoperative pain or other symptoms following operative intervention, which remained true at recent follow-ups. Temporary/mild improvement of symptoms included all of the remaining patients. These patients largely experienced symptomatic improvement similar to the significantly improved cohort, but over the course of months to years experienced a progressive return of symptoms, resulting in a clinical status similar to or only mildly improved from their preoperative state. A small minority of the patients in this cohort only ever reported a minor improvement of symptoms that did not significantly improve functional status, but which was noticeable and consistent at recent follow-ups.

RESULTS

Patient demographics, diagnoses, and clinical outcomes

Sixty-seven patients met the inclusion and exclusion criteria, 94% of whom were female with an average age of 33.1 years (range: 18–60 years). These patients underwent an average of 2.1 neurosurgical procedures with nearly half of our cohort undergoing only 1 operation. The average follow-up was 32.9 months. Age was determined based on age during the first neurosurgical operation with the senior author (FAS), and follow-up length was determined as the time from the first neurosurgical operation with the senior author to the time of the most recent follow-up appointment. Table 1 also highlights common preoperative diagnoses with 65.7% of patients having a Chiari malformation, 85.1% having craniocervical and/or AAI, and 17.9% having tethered cord syndrome. These were calculated as diagnoses before any of the neurological operations the patients underwent, not necessarily diagnoses received before their first operation. Furthermore, 67.2% of patients were determined to have experienced significant symptomatic improvement by the most recent follow-up appointment, while 23.4% of patients experienced mild or temporary improvement during their operations and follow-up. Only 9.4% of patients failed to symptomatically improve as a result of their neurosurgical operations.

Operation characteristics

The 67 patients included underwent a total of 138 neurosurgical procedures, 115 of which were conducted by the senior author. The remaining 23 operations were conducted by other neurosurgeons at outside institutions. Of the procedures conducted at outside institutions, the most common was a suboccipital craniectomy (SOC), accounting for 13 of the 23 operations. A full breakdown of the neurosurgical procedures conducted at outside

Table 1: Demographic, Diagnostic, and Outcome Measures for Neurosurgical EDS Patients

Patient Characteristics	% Applicable
% Female	94.0% (n=63)
Average Age (years)	33.1 (range: 18-60)
Average # Neurosurgical Operations	2.1 (range: 1-8)
% 1 Operation	47.8% (n=32)
% 2 Operations	25.4% (n=17)
% 3+ Operations	26.9% (n=18)
% with Chiari Malformation	65.7% (n=44)
% with CCI and/or AAI	85.1% (n=57)
% with Tethered Cord Syndrome	17.9% (n=12)
Average Follow-up (months)	32.9 (range: 0-87)
% Significant Improvement of Symptoms	67.2% (n=43)
% Temporary/Mild Improvement of Symptoms	23.4% (n=15)
% Continuation of Symptoms	9.4% (n=6)

Table 2: Neurosurgical Operations Conducted at Outside Institutions and their Outcomes

Procedure	# Conducted	% Needing revision surgery
SOC	13	100% (n=13)
OCF (O-C2)	1	100% (n=1)
SOC + Cervical Fusion	1	100% (n=1)
Cervical Fusion	4	50% (n=2)
C1-2	1	100% (n=1)
C4-5	1	0% (n=0)
C4-7	1	0% (n=0)
C4-T1	1	100% (n=1)
Other	4	0% (n=0)
L5-S1 Fusion	2	0% (n=0)
T12-L1 Laminotomy	1	0% (n=0)
C2 Ganglionectomy	1	0% (n=0)
Total	23	73.9% (n=17)

institutions can be found in Table 2. Of these 23 procedures, 17 of them, or 73.9%, required revision surgeries. This included all 13 SOC, along with 4 of the other 10 procedures. All 17 revision cases were the result of continued or returning symptoms, with 2 cases (11.8%) also involving pseudoarthrosis. Immediate postoperative complication rates were not calculated for these procedures as detailed clinical notes from the outside institutions were not available.

Of the 115 operations by the senior author, the vast majority fell into the following categories: SOC; OCF; SOC with OCF; cervical fusion; SOC with cervical fusion; odontoidectomy; or tethered cord release. The full breakdown of procedure types is shown in Table 3. Of these 115 cases, there were 4 instances with postoperative complications, amounting to 3.5% of cases. Postoperative complications were defined as injuries or deleterious clinical consequences directly related to the operation in the immediate to near postoperative period. These included 2 pseudomeningoceles, 1 wound infection,

1 cerebrospinal fluid (CSF) leak, and 1 partial-thickness durotomy, with 1 case resulting in both a pseudomeningocele and a wound infection. Further, of the 115 cases, 20 required a revision procedure amounting to 17.4% of cases. For the 20 revisions, 15 of the procedures, or 75%, were needed to address continued or returning symptoms, with 9 cases (45%) involving pseudoarthrosis. In addition, 6 of the revisions, or 30%, were needed to address postoperative complications. The following case illustrations give further insight into the symptoms, procedures, and outcomes these patients experienced.

Case illustrations

Case 1

Patient 1 is a 31-year-old woman with a history of EDS who presented with headaches and neck pain. She reported severe daily neck pain associated with shoulder pain, along with numbness of all 4 limbs and occasional radicular pain

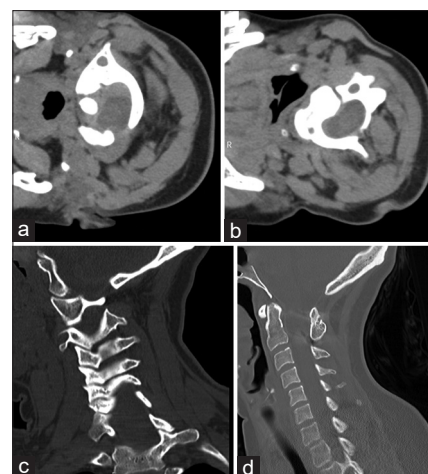


Figure 1: Case 1 imaging - Atlantoaxial instability. (a-c) Preoperative cervical rotational CT turned to the right with C1 axial view. (a) C2 axial view (b) and sagittal view. (c) Demonstrating 45° rotation of C1 on C2. (d) 19-months postoperative sagittal cervical CT demonstrating expected postoperative changes of a C1-2 posterior cervical fusion. CT: Computed tomography

Table 3: Neurosurgical Operations Conducted by the Senior Author and their Outcomes

Procedure	# Conducted	% w/Post-Op Complications	% Needing Revision Surgery
SOC only	6	16.7% (n=1)	0% (n=0)
SOC + OCF	17	0% (n=0)	17.6% (n=3)
SOC + O-C2	16	0% (n=0)	12.5% (n=2)
SOC + O-C3	1	0% (n=0)	100% (n=1)
OCF	18	11.1% (n=2)	27.8% (n=5)
O-C2	14	14.3% (n=2)	28.6% (n=4)
O-C3	2	0% (n=0)	0% (n=0)
O-C4	2	0% (n=0)	50% (n=1)
SOC + C1-2 Fusion	15	0% (n=0)	6.7% (n=1)
Cervical Fusion	30	0% (n=0)	20% (n=6)
C1-2	17	0% (n=0)	23.5% (n=4)
C1-T2	1	0% (n=0)	0% (n=0)
C2-6	1	0% (n=0)	0% (n=0)
C3-4	1	0% (n=0)	0% (n=0)
C4-5	1	0% (n=0)	0% (n=0)
C4-6	2	0% (n=0)	50% (n=1)
C5-6	2	0% (n=0)	0% (n=0)
C5-7	2	0% (n=0)	0% (n=0)
C5-T1	1	0% (n=0)	100% (n=1)
C6-7	2	0% (n=0)	0% (n=0)
Odontoidectomy	5	20% (n=1)	20% (n=1)
Transoral	4	0% (n=0)	0% (n=0)
Transnasal	1	100% (n=1)	100% (n=1)
TCR	12	0% (n=0)	0% (n=0)
Other	12	0% (n=0)	33.3% (n=4)
L5-S1 Fusion	3	0% (n=0)	0% (n=0)
SI Joint Fusion	3	0% (n=0)	33.3% (n=1)
R L4-5 Laminoforaminotomy	1	0% (n=0)	0% (n=0)
VP shunt	3	0% (n=0)	33.3% (n=1)
Pseudomeningocele Repair	1	0% (n=0)	100% (n=1)
Incision and Drainage	1	0% (n=0)	100% (n=1)
Total	115	3.5% (n=4)	17.4% (n=20)

down her arms and back. She also reported daily headaches on awakening that were partially alleviated by wearing a cervical collar. She occasionally experienced slurred speech as well. These symptoms, especially the neck pain, were present since childhood. She reported that lying flat helped relieve her pain, but this prevented her from being able to function normally. Despite multiple medication options for pain management, she did not experience significant relief and reports constant pain at a 7 out of 10 intensity at baseline. Neurological examination revealed a positive right Hoffman's sign and equivocal left Hoffman's sign, along with trouble completing a tandem gait. Magnetic resonance imaging (MRI) and computed tomography (CT) imaging studies suggested AAI, with rotational CT scans illustrating increased rotation of C1 on C2 [Figure 1a-c]. She then underwent a C1-2 posterior spinal instrumentation and fusion without complication.

After her procedure, she reported improvement in her symptoms. Specifically, she experienced a sharp decrease in her headaches and no longer feeling as though she had to intentionally hold her head up. The improvement of her symptoms has been consistent since her procedure and remained true at her most recent follow-up, 14 months

after her initial procedure, with subsequent 19-month postoperative CT scans showing stable fusion with expected postoperative changes [Figure 1d]. This patient was categorized as having experienced a significant improvement in symptoms.

Case 2

Patient 2 is a 41-year-old woman with a history of EDS who presented with headaches and neck pain. The pain had been present for a few years and progressively worsened over the last year. She described the pain as daily and limiting her ability to get out of bed. She states the pain is worsened by the extension of her neck. The pain is a 7 out of 10 in intensity at baseline, with flares up to 9 out of 10, and it is associated with accompanying dizziness and vision changes that she describes as seeing stars. She had attempted to manage the pain with various medications along with physical therapy, acupuncture, chiropractic therapy, and massage therapy with results ranging from short-term mild relief to worsening pain. Physical examination was significant for demonstrating a wide-based gait, increased deep tendon reflexes in all four extremities, bilateral ankle clonus, and bilateral positive Hoffman's signs. CT and MRI imaging identified a Chiari malformation with descent of the tonsils below the ring of C1, along with compression at the foramen magnum and a right-sided arachnoid cyst posterior to the cerebellum. Dynamic imaging demonstrated acute CXA $<130^\circ$ with some retroflexion of the dens [Figure 2a and b]. She then underwent an elective

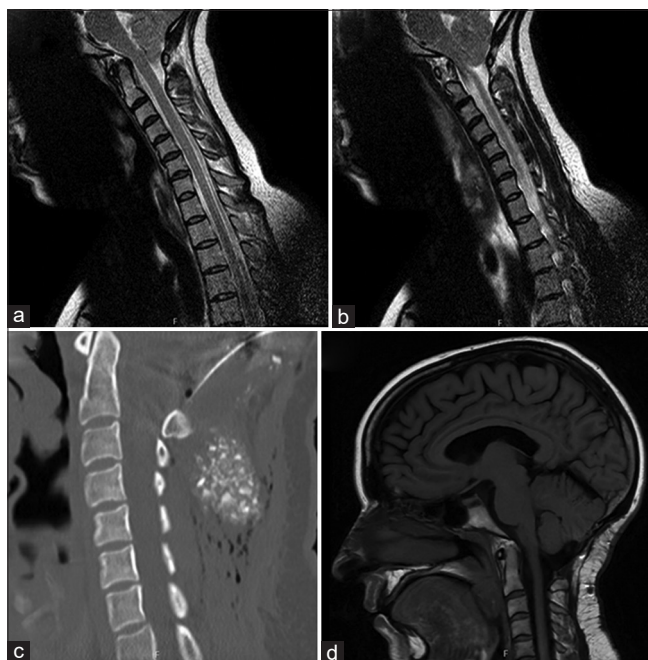


Figure 2: Case 2 imaging - Chiari malformation and craniocervical instability. (a and b). Preoperative T2-weighted sagittal cervical MRI demonstrating cerebellar tonsillar herniation below the ring of C1 and acute clivoaxial angle $<130^\circ$. (c) One-day postoperative sagittal cervical CT demonstrating expected postoperative changes of a SOC and O-C2 fusion. (d) Postoperative sagittal T1-weighted flair MRI brain 67 months after initial operation and 15 months after C6-7 fusion demonstrating expected postoperative changes of a SOC and O-C2 fusion. MRI: Magnetic resonance imaging, CT: Computed tomography, SOC: Suboccipital craniectomy

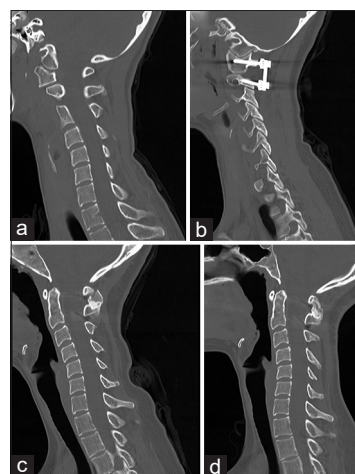


Figure 3: Case 3 imaging – Pseudoarthrosis (a) Preoperative sagittal rotational cervical CT turned to the left which demonstrates rotational subluxation in conjunction with axial views not shown. (b and c) Postoperative sagittal cervical CT 24 months after initial operation demonstrating pseudoarthrosis with bone graft incorporated into the C2 lamina but without bridging bone between C1 and the bone graft. (d) Postoperative sagittal cervical CT 47 months after the initial operation and 18 months after revision surgery demonstrating bony fusion and expected postoperative changes from a C1-2 posterior fusion. CT: Computed tomography

SOC and O-C2 posterior spinal instrumentation and fusion without complication.

Following her procedure, she reported near-resolution of her symptoms for approximately the first few months [Figure 2c]. At this point, she began to report neck spasms that remained stable for the following years and were accompanied by stable radiographic and physical examinations. Four years after her initial procedure, she presented with upper back and shoulder pain with radiographic evidence of multilevel cervical disc disease and resulting foraminal stenosis. After she failed to improve with epidural steroid injections and physical therapy, she elected to undergo a C6-7 anterior cervical discectomy and fusion without complication, 52 months after her initial procedure. She reported continued neck and shoulder pain at her most recent follow-up, 64 months after her initial procedure and 12 months after her C6-7 fusion; however, the severity of these symptoms remains reduced compared to preoperatively, with intensity rated as 3 out of 10 at baseline with flares up to a 7 out of 10 in intensity. The patient reports that despite her continued pain, she is glad she had the procedures and feels she is somewhat improved. Subsequent postoperative imaging illustrates stable fusion with expected postoperative changes [Figure 2d]. This patient was categorized as having experienced a temporary/mild improvement of symptoms.

Case 3

Patient 3 is a 22-year-old woman with a history of EDS who presented with several years of progressive headaches and neck pain. Her pain was accompanied by numbness of her hands and feet, nausea, gait instability, and was aggravated by flexion and extension of her neck. At the initial presentation, her pain was a 3 out of 10 in intensity and nonresponsive to multiple previous medications. A hard cervical collar trial helped alleviate her headaches. Her symptoms worsened over

the following 6 months, with pain becoming more constant and reaching a 5 out of 10 intensity. She also developed weakness in her upper extremities, right worse than left, resulting in commonly dropping objects. Her balance and coordination also worsened with associated lower extremity fatigue and feeling that her legs would give out from under her. Her sensation of tingling also spread from her hands to include her shoulders. Dynamic CT imaging demonstrated C1-2 rotational subluxation worse when turned to the left that was suggestive of AAI [Figure 3a]. She elected to undergo a C1-2 posterior spinal instrumentation and fusion, which was done without complication.

Following her procedure, she reported improvement in her symptoms which lasted for the first few months. At this point, her symptoms began to return. Further, over time her postoperative CT scans began to demonstrate pseudoarthrosis at C1-2 by demonstrating that while the bone graft incorporated into the C2 lamina, bridging bone did not fully form between the C1 lamina and the bony graft [Figure 3b and c]. An external bone stimulator was utilized in an attempt to nonoperatively stimulate fusion, but this did not improve the fusion mass. Her pain returned to the preoperative 5 out of 10 intensity. At this point, she elected to undergo a C1-2 fusion revision, which occurred 29 months after her initial procedure. During this procedure, she was found to have an incomplete fusion between C1 and the bone graft, so the senior author proceeded to decorticate the C2 lamina and ring of C1 before adding additional bone graft posterolateral to C1-2 with additional bone morphogenic protein.

Following this procedure, the patient's symptoms improved and remained stable. At her most recent follow-up, she continued to have headaches and neck pain, but significantly milder in comparison to preoperative symptoms. Her symptoms and radiographic studies have remained stable at 48 months after her index procedure and 19 months after her

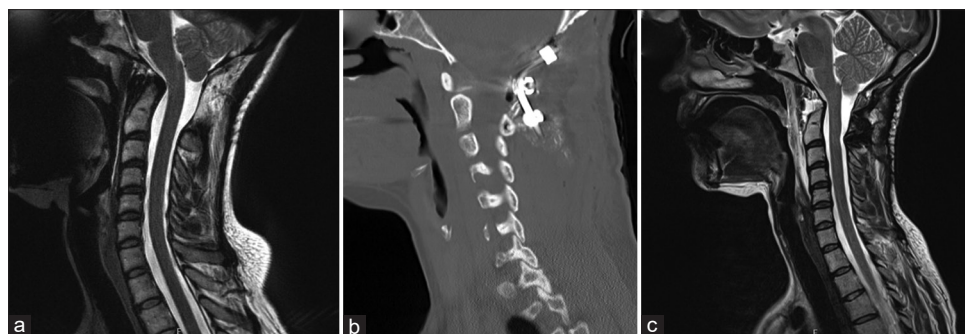


Figure 4: Case 4 imaging – Odontoidectomy (a) Preoperative T2-weighted sagittal cervical MRI demonstrating restricted CSF flow posterior to the cerebellum, pannus formation posterior to the dens, a slightly retroflexed odontoid process, and slight kinking of the anterior brainstem. (b) Postoperative sagittal cervical CT 1-day after OC2 fusion demonstrating expected postsurgical changes. (c) Postoperative T2-weighted sagittal cervical MRI 10 months after O-C2 fusion and 1-day after odontoidectomy showing expected postsurgical changes. MRI: Magnetic resonance imaging, CSF: Cerebrospinal fluid, CT: Computed tomography

revision, with imaging at that time demonstrating adequate fusion and expected postsurgical changes [Figure 3d]. This patient was categorized as having experienced a significant improvement in symptoms.

Case 4

Patient 4 is a 37-year-old woman with a history of EDS who presented with neck pain along with headaches and bilateral arm pain. She reported the pain had been ongoing since childhood, but steadily worsening, especially over the last decade. The pain was now a 7 out of 10 and precluded her from working as lying down was one of the only things found to give her relief. She described the pain as crushing, pounding, and burning. A previous neurosurgical workup at an outside institution identified a Chiari malformation and a retroflexed odontoid process. She previously underwent a SOC and C1 laminotomy for the treatment of her Chiari. MRI imaging demonstrated restricted CSF flow posterior to the cerebellum, pannus formation posterior to the dens, a slightly retroverted odontoid process, and slight kinking of the anterior brainstem [Figure 4a]. Given her symptoms and these findings, she elected to undergo an O-C2 posterior spinal instrumentation and fusion, which was done without complication and with follow-up imaging demonstrating expected postoperative changes [Figure 4b].

Following this procedure, the patient reported symptomatic improvement that was consistent for approximately 10 months. At that time, her symptoms returned quite suddenly and severely. MRI imaging demonstrated basilar invagination and anterior compression of the brainstem with CSF flow blocked anterior to the brainstem and posterior to the dens. Unfortunately, the MRI imaging from this time is unavailable in our electronic health record for inclusion in this manuscript. She then underwent an endoscopic transoral odontoidectomy in conjunction with otolaryngology.

Following the odontoidectomy, the patient reported an immediate improvement in her symptoms with imaging demonstrating expected postsurgical changes [Figure 4c]. At follow-up 1 month after the odontoidectomy and 15 months after her initial procedure at our institution, she reported significant symptomatic improvement. The patient lived far from our institution and did not return for subsequent follow-up. This patient was categorized as having experienced a significant improvement in symptoms.

Case 5

Patient 5 is a 23-year-old woman with a history of EDS who presented with neck pain and headaches associated with dizziness and occasional bilateral lower extremity numbness. The pain was constant and 7 out of 10 in intensity and regularly prevented her from sleeping. A cervical collar trial period provided some symptomatic relief, but the pain continued to worsen. Over the ensuing 2 years, her symptoms progressively worsened with pain causing multiple trips to the emergency room. Physical therapy and injections were unsuccessful in managing her pain. Her pain increased to an 8 out of 10 and was aggravated by movement. MRI imaging demonstrated a Chiari malformation with 5 mm of tonsillar herniation below the foramen magnum and anterior kinking of the brainstem from mild basilar impression and C2 pannus formation, along with suspected CCI based on flexion/extension imaging [Figure 5a]. She elected to undergo a SOC and an O-C2 posterior spinal instrumentation and fusion, which were completed without complication.

Following this procedure, the patient reported significant improvement in her symptoms with only minimal pains remaining. However, the patient did develop lower back pain, leg spasms, and urinary incontinence that went on to require the use of a catheter. Urodynamic testing consistent with neurogenic bladder and normal MRI imaging led to a

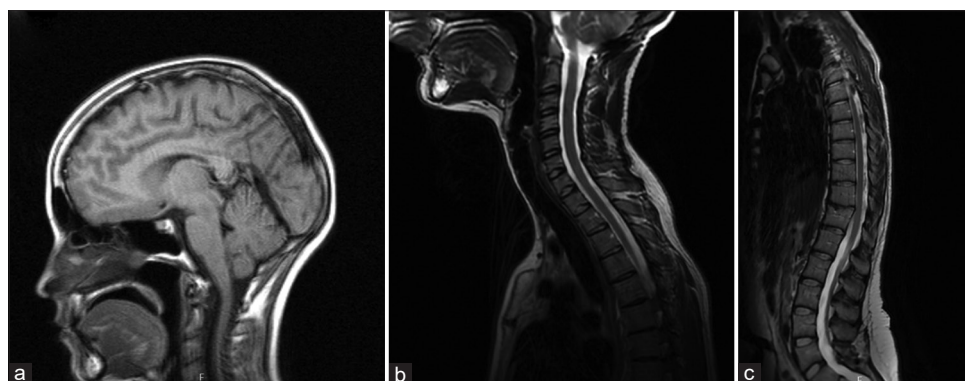


Figure 5: Case 5 imaging - Tethered cord release. (a) Preoperative T1-weighted sagittal MRI brain demonstrating 5 mm of tonsillar herniation below the foramen magnum and anterior kinking of the brainstem from the mild basilar impression and C2 pannus. (b and c) Postoperative T2-weighted sagittal cervical MRI 64 months after the initial operation and 36 months after tethered cord release demonstrating expected postoperative changes. MRI: Magnetic resonance imaging

suspicion for an occult tethered cord and the patient elected to undergo an L5 laminectomy for tethered cord release.

Postoperatively, the patient's urinary symptoms improved. While these symptoms did not abate completely, she continued to report improvement from preoperative state at follow-up, with imaging demonstrating expected postoperative changes [Figure 5b and c]. At the most recent follow-up, 66 months after her initial procedure and 38 months after her tethered cord release, she continued to endorse significant improvements in all of her symptoms from their preoperative states. This patient was categorized as having experienced a significant improvement of symptoms.

DISCUSSION

EDS is a connective tissue disorder resulting in hypermobile joints and fragile tissues. All of the patients in our retrospective analysis had a preexisting diagnosis of EDS. This diagnosis was made by outside physicians before the patients underwent surgery with our senior author based on clinical examination, along with some patients having a positive family history and/or having previously undergone genetic testing. The Beighton score was used as a confirmatory check on this existing diagnosis. The Beighton score is a set of maneuvers in a nine-point scoring system that measures joint hypermobility.^[10] While the Beighton score does not itself provide a definitive diagnosis of EDS, it does provide an objective measure of hypermobility which is useful for an EDS diagnosis.^[10–12] This score, in conjunction with clinical presentation and clinician judgment, can be used to make a suggestive diagnosis of EDS, which can be corroborated with family history and solidified with genetic testing.^[10–12] The gender proportion of patients in this study was overwhelmingly female and younger than would be otherwise expected for neurosurgical patients. Considering females are more likely to have connective tissue disorders, and the idea that EDS would wear down ligamentous tissue faster than in other individuals, these differences make sense in the context of this study.

Existing literature suggests a relationship where patients with EDS are more likely to develop a Chiari malformation.^[1,3,4,13] Over 65% of the patients in this study received a diagnosis of a Chiari malformation. These patients generally presented with debilitating headaches, especially in the occipital region or base of the skull. Many of these patients also presented with neck pain. Patients 2 and 5 highlight these presenting symptoms and the pursued management strategies. Chiari malformations were diagnosed through radiographic

imaging and treatment was generally pursued with SOC, sometimes in conjunction with either C1-2 fusion or OCF. Many of these patients were initially treated with SOC at an outside institution, with 100% of those 13 patients requiring a revision procedure with the senior author. The need for revision was generally the result of developing CCI or AAI, and the revisions carried out involved OCF or C1-2 posterior fusion. Patient 4 illustrates the need for revision after a SOC and the resulting management. These findings are particularly interesting in the context of recent literature suggesting that AAI may be the point of pathogenesis in CM 1s.^[14] Recent literature has suggested that AAI may be the cause of symptomatic CM 1s, and suggests that treatment of the AAI itself may be required instead of the traditionally accepted decompressive procedures.^[14] While further study into Chiari malformations and AAI broadly is necessitated, it stands to reason that EDS patients would be at increased risk of instability given their underlying connective tissue deficiencies. Thus, this existing literature potentially supports the consideration of utilizing stabilization procedures when treating Chiari malformations in patients with EDS.

During radiographic and clinical evaluation, signs of AAI or CCI prompted the senior author to consider stabilization via C1-2 fusion or OCF in addition to the SOC procedure. The clinical and radiographic evidence for AAI or CCI is further discussed in subsequent paragraphs. Six patients received SOC alone from the senior author, none of whom required revision. Three of seventeen patients who underwent SOC and OCF with the senior author required revision, along with one of fifteen who underwent SOC and C1-2 fusion. These revision rates are far smaller than those for the patients receiving a SOC alone at an outside institution. This again highlights the importance of assessing EDS patients with Chiari malformations for signs of CCI or AAI, and potentially modifying surgical management to include C1-2 fusion or OCF to mitigate the possible need for additional stabilization surgery in these patients.

Mechanical laxity has been found in the craniocervical junction of patients with EDS, along with irregular displacement of the spinal cord during head movements.^[2] The connection between EDS causing ligamentous laxity resulting in AAI or CCI is also becoming more well-established in the existing literature.^[1–3,6,15,16] Over 85% of the patients in this study were diagnosed with either CCI or AAI. These instabilities often occurred in conjunction with or following Chiari diagnosis and treatment, while in other patients the instability diagnoses were occurring without a concomitant Chiari malformation. The relative frequency of CCI and AAI in this patient cohort is also highlighted by the number of OCF and C1-2 fusions conducted in this study, either alone

or in conjunction with a SOC. These findings are especially interesting in the context of the novel clinical entity that has been described as central AAI or dislocation. In this clinical phenomenon, the atlantodental interval may not be altered abnormally and there may not be compression of neural structures by the odontoid process; however, facet instability is still present.^[17,18] In the studies describing this phenomenon, treatment of the instability leads to a reduction in symptoms, and it has been surmised that this instability may be contributory to many pathologies that afflict the craniocervical region.^[17,18] As such, it stands to reason that EDS could be an additional contributing factor to the development of this instability, again highlighting the need to potentially consider stabilization procedures in EDS patients presenting with craniocervical symptoms.

The patients all illustrate some of the common symptoms of these instabilities along with the pursued management strategies. These patients generally presented with debilitating neck pain and headaches that were focused near the base of the skull and exacerbated by extension/flexion and/or rotational neck movement. These patients generally had undergone several attempts at medical pain management through pain specialists involving several different medication options. Some patients also attempted physical therapy or steroid injections to address their pain. Further, trials of hard cervical collars often provided relief, suggesting that the symptoms were arising from instability and could be mitigated by fusion. Radiographic studies were pursued, which suggested instability by demonstrating angular displacement on rotational imaging or an acute CXA, which is discussed further in subsequent paragraphs. Surgery was reserved for patients with severe unrelenting pain or other symptoms that were debilitating in preventing normal functional capacity, and surgery was only then performed when radiographic evidence supported the decision.

The management strategy for EDS patients with CCI/AAI, either independently or in conjunction with a Chiari malformation, has been a subject of debate in recent literature.^[6,9,19-21] Previous studies published by the authors of this manuscript have argued that the CXA is a helpful indirect metric for CCI.^[6,21] These studies have found that OCF is an effective management strategy for CCI in the setting of previous SOC, successfully correcting acute CXA and resulting in symptomatic relief.^[6,21] The results of this study corroborate that OCF or C1-2 fusion can be effective for many EDS patients with CCI or AAI; however, the need for revision procedures following a significant number of these procedures provides further evidence for the unique challenges in treating EDS patients. Given the baseline tissue fragility and hypermobility

these patients demonstrate, it is not surprising that revision rates may be higher than otherwise expected.

Some of the revisions needed for these procedures were the result of pseudoarthrosis or anterior brainstem compression. Pseudoarthrosis generally presented with return of preoperative symptoms and was corroborated by the lack of fusion demonstrated in radiographic findings. While there is a dearth of literature directly connecting EDS to pseudoarthrosis, it stands to reason that a condition that results in aberrant wound healing may make it more difficult to achieve adequate fusion. These cases were revised with revision fusion operations to achieve adequate long-term fusion. Moreover, the laxity of tissues in these patients may have accounted for the development of anterior brainstem compression in a small number of patients who went on to require odontoidectomy. These specific patients developed a rapid return of symptoms with radiographic findings of brainstem compression. At this point, surgery was deemed immediately necessary. In most cases, a transoral approach was taken and was quite successful. One case of transnasal odontoidectomy was attempted and required revision with a transoral odontoidectomy. Patients 3 and 4 further highlight these complications and how they were addressed. Moreover, there were also a small number of revisions needed to address complications, which can help explain a portion of these rates. Between the revisions for complications, pseudoarthrosis, and brainstem compression, many of the revisions are accounted for; nevertheless, the overall high revision rates in addressing CCI or AAI confirm that EDS patients face unique challenges in postoperative healing that require further study and possible changes in future approaches based on emerging evidence.

Moreover, while the connection between tethered cord syndrome and EDS is less well established, evidence continues to emerge that this relationship exists and may be caused by EDS-induced disease of the filum terminale.^[1,5,7] Tethered cord presented in these patients as demonstrated by patient 5. Urinary symptoms were the defining symptom with back and leg pain or other debilitations present as well. Urodynamic testing and radiographic imaging led to suspicion for a tethered cord and surgery was pursued with lumbar laminectomy for tethered cord release. These procedures resulted in no complications or revisions. The relative frequency of these cases further supports the evidence that there is a relationship between EDS and tethered cord syndrome, and the lack of revisions or complications may suggest that this relationship does not result in the same degree of tissue laxity seen in the occipital and cervical regions of EDS patients.

Additional neurosurgical procedures in this patient cohort were largely heterogeneous. Some defining categories included additional cervical fusions at levels other than C1-2, lumbosacral fusions, and sacroiliac fusions. These surgeries were indicated for a diverse set of preoperative diagnoses including disc herniations and stenosis. While the heterogeneity of the procedures and diagnoses may make it challenging to draw firm conclusions, the propensity to require surgery at cervical levels along with the lumbosacral and sacroiliac junctions may highlight additional areas of heightened laxity in addition to the craniocervical and atlantoaxial junctions.

Overall, an analysis of EDS patients receiving neurosurgical care highlights the relationship between EDS and Chiari malformations, CCI or AAI, and tethered cord syndrome, while also suggesting possible links to laxity throughout the rest of the cervical spine, the lumbosacral junction, and the sacroiliac junction. Specifically, a predisposition to occipitocervical region instability should prompt neurosurgeons to assess EDS patients with Chiari malformations or other issues in this region for signs of AAI or CCI, and possibly to add OCF or cervical fusion procedures to their treatment plan based on that assessment. This analysis also suggests that this patient group may be more prone to pseudoarthrosis and anterior brainstem compression, resulting in the need for revision procedures at a higher rate than would otherwise be expected. However, the management strategies pursued were largely effective in significantly relieving symptoms for the majority of patients and provided temporary or mild relief for most of the remaining patients, while producing few direct postoperative complications.

Limitations of this study include its retrospective nature and focus on a single institution for most of its data collection. Further, given the study is retrospective, there remains a risk of bias in the selection for surgical intervention. In addition, the lack of detailed records from outside institutions where patients in this series received additional neurosurgical intervention results in a lack of complete data on those cases. Furthermore, a lack of consistent follow-up in some of the patients produces a challenge in following the outcomes of the neurosurgical interventions, while an inability to locate certain radiographic images from these cases makes reporting case illustrations more challenging. Finally, we recognize these limitations along with subjective outcome measurements reduce the ability to draw quantitative conclusions from this study; however, we believe the data and individual cases provide a qualitative and descriptive narrative of neurosurgery on EDS patients that provides unique insight into the topic and can help direct future study into this unique patient population.

CONCLUSIONS

EDS is associated with a diverse set of neurological complications including Chiari malformations, CCI, AAI, and tethered cord syndrome. Current neurosurgical treatment strategies are safe and largely effective in symptomatic management but may require additional revisions due to distinct issues that arise in the care of this patient population. This connective tissue disease results in unique challenges for neurosurgical intervention associated with a patient predilection for instability, especially in the occipitocervical region. This should prompt neurosurgeons to carefully evaluate EDS patients for CCI or AAI in the setting of Chiari malformations or other occipitocervical concerns and to consider OCF or cervical fusion as part of the treatment paradigm for these patients to address that instability without the need for a revision procedure.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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