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Narrative Review

Craniocervical instability in patients with Ehlers-Danlos syndrome: controversies in diagnosis and management

Gordon Mao, MD, Srujan Kopparapu, MD, Yike Jin, MD, A. Daniel Davidar, MBBS, Andrew M. Hersh, AB, Carly Weber-Levine, BS, Nicholas Theodore, MD*

Department of Neurosurgery, Johns Hopkins University School of Medicine, , 600 N. Wolfe St., Meyer 7-113, Baltimore, MD 21287, USA

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Abstract Ehlers-Danlos syndrome (EDS) is a rare hereditary condition that can result in ligamentous laxity and hypermobility of the cervical spine. A subset of patients can develop clinical instability of the craniocervical junction associated with pain and neurological dysfunction, potentially warranting treatment with occipitocervical fixation (OCF). Surgical decision-making in patients with EDS can be complicated by difficulty distinguishing from hypermobility inherent in the disease and true pathological instability necessitating intervention. Here we comprehensively review the available medical literature to critically appraise the evidence behind various proposed definitions of instability in the EDS population, and summarize the available outcomes data after OCF. Several radiographic parameters have been used, including the clivo-axial angle, basion-axial interval, and pB-C2 measurement. Despite increasing recognition of EDS by spine surgeons, there remains a paucity of data supporting proposed radiographic parameters for spinal instability among EDS patients. Furthermore, there is a lack of high-quality evidence concerning the efficacy of surgical treatments for chronic debilitating pain prevalent in this population. More standardized clinical measures and rigorous study methodologies are needed to elucidate the role of surgical intervention in this complex patient population.

Keywords: Craniocervical instability; Ehlers-Danlos syndrome; Hypermobility; Occipitocervical fixation; Occipitocervical fusion; Spinal instability

Introduction

The craniocervical junction (CCJ) is the most mobile portion of the spine, capable of flexion, extension, and lateral rotation [1]. The CCJ is composed of the occiput (C0), atlas (C1), axis (C2), and associated ligaments and muscles [2–4]. Its complex structure allows it to achieve a high degree of mobility while maintaining mechanical stability, defined by White et al. in 1975 as "the ability of the spine to limit its patterns of displacement under physiologic loads so as not to damage or irritate the spinal cord or nerve roots" [5,6]. Conversely, mechanical instability leads to abnormal motion that can impinge on neural elements and threaten neurological function. Given the location and the critical functions of the CCJ, craniocervical instability (CCI) can result in neurological symptoms, cervicomedullary compression, neurovascular injury, or death [7]. CCI can manifest as abnormal motion including horizontal or vertical atlantoaxial subluxation, occipitoatlantal translation, and basilar invagination, also known as atlantoaxial

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*Corresponding author. Department of Neurosurgery, Johns Hopkins University School of Medicine, 600 N. Wolfe St., Meyer 7-113, Baltimore, MD 21287, USA. Tel.: (410) 550-5463; fax: (410) 502-3399.

E-mail addresses: theodore@jhmi.edu, prender14@gmail.com (N. Theodore).

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impaction or cranial settling [8]. Basilar invagination may cause ventral brainstem compression (VBSC) and associated paresthesias, weakness, and hyperreflexia [9].

Although trauma is the most common etiology of CCI, connective tissue diseases (CTDs) have also been implicated, including congenital osseous malformations of the CCJ [8] and osteoligamentous autoimmune diseases [10]. In particular, Ehlers-Danlos syndrome (EDS) has generated significant concern for CCI [11]. EDS is an inherited CTD that affects collagen synthesis, resulting in vascular and skin fragility, ligamentous and joint laxity, and frequent dislocations and subluxations [12–14]. CCI in EDS is thought to arise from ligamentous laxity at the CCJ resulting in neural compression and injury [9,15–17]. However, the assessment of clinical instability is not always straightforward, and only a minority of patients with EDS develop neurological injury secondary to hypermobility, although the exact prevalence is unclear [9]. The benign hypermobility of EDS featuring increased range of joint movement can cause transient neurological symptoms and is often mistakenly classified as CCI, although surgical intervention is not necessarily warranted. In contrast, true instability presents a major risk of permanent deficits or death [18].

Consensus is lacking in the literature on the decision-making for craniocervical surgery in patients with EDS due to the difficulties in diagnosis of instability compared with hypermobility and the small sample sizes reported in the literature. Several radiographic and clinical measurements have been proposed to distinguish instability and hypermobility; however, their ability to reflect underlying spinal instability is debated. Here we review the literature on CCI in patients with EDS, focusing on diagnostic workup, treatment paradigms, and discrepancies in the literature.

Diagnosis of CCI in patients with EDS

Beyond the traditional modalities of radiography, static MRI, and high-resolution computed tomography (CT) of the CCJ, newer techniques such as dynamic (functional) and physiologically loaded (positional, upright) imaging may assist in the evaluation of CCI. Dynamic CT imaging includes flexion and extension CT, in which the patient flexes their neck toward their head as much as possible without causing pain or discomfort and then extends their head backwards. Passive manipulation can be performed by the examiner if the patient is unable to actively perform these maneuvers [19,20]. Dynamic CT is not routinely performed, and rigorous studies are lacking on its validity for assessment of CCI. Da Silva et al. suggest that it can help in the workup of CCI in patients with congenital malformations of the craniovertebral junction; however, its sensitivity and specificity in the EDS cohort is unclear [21].

In general, 3 key morphometric variables have been well described, namely the clivo-axial angle (CXA), the basion-axial interval (BAI), and the Grabb, Mapstone, and Oakes measurement [9].

Clivo-axial angle

The CXA is defined by the angle between the clivus line, connecting the top of the dorsum sellae to the basion, and the posterior axial line, running from the inferodorsal to the most superodorsal part of the dens (Fig. 1A). Some have instead used a line drawn through the mid-portion of the odontoid and a line drawn along the lower third of the clivus from the spheno-occipital synchondrosis to the basion. In individuals without instability, the CXA generally ranges from 145° to 160° [10,22]. Nagashima and Kubota reported a series of 41 normal adults with mean CXA of 158°±10°, noting that flexion increased the CXA by 9° to 11° and extension decreased the CXA by a similar amount [23]. Botelho et al. compared 33 patients lacking pathology with 48 patients with a Chiari malformation type 1 (CM-1) and 25 patients with basilar invagination. The asymptomatic cohort had a mean CXA of 148°±10°, similar to the CM-1 group with a CXA of 150°±12°, but significantly greater from the basilar invagination group CXA of 120° [24]. Patients with rheumatoid arthritis (RA), who are at higher risk for CCI than the general population, typically have a CXA ranging from around 135° in flexion to 175° in extension [25].

Vangilder et al. suggested that a CXA <150° may be associated with ventral cord compression [26], and Nagashima

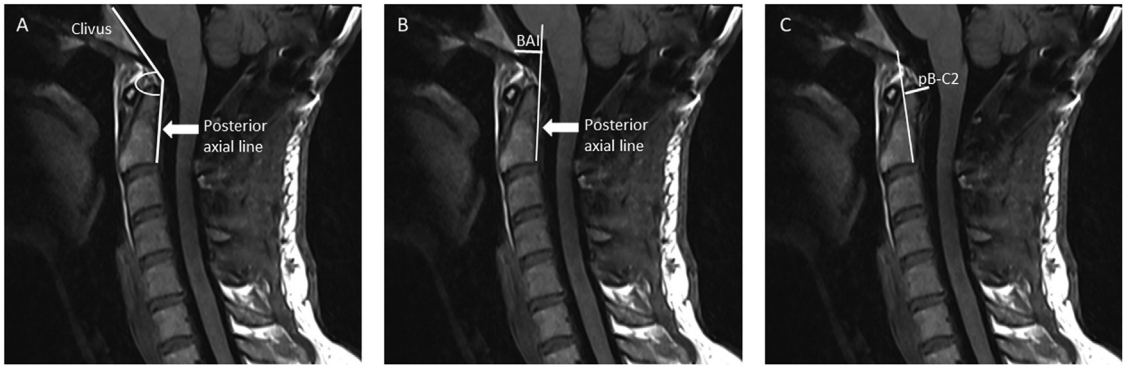

Fig. 1. T1-weighted sagittal MRI of the craniocervical junction in a patient with EDS depicting A) clivo-axial angle, B) basion-axial interval, and C) and the pB-C2 measurement.

and Kubota reported that a CXA <130° may produce VBSC, and therefore surgical fusion should increase the CXA [23]. Several authors have proposed 135° as a pathological cutoff [24,27–29]. Decreasing CXA and increasing kyphosis of the CCJ has been shown to cause compression of the cervicomedullary junction in other syndromes of CCI, resulting in progressive neurologic deficits [30].

Basion-axial interval

Another common metric is the BAI, also known as the horizontal Harris measurement, defined by the distance from the basion to the posterior axial line (Fig. 1B) [31]. Harris et al. examined radiographs of 400 adults and 50 children lacking instability, finding that 98% of the adults and all children had a BAI <12 mm [31]. Consequently, instability is indicated when the BAI exceeds 12 mm. BAI measures the dynamic translation between the basion and axis and was validated in CT scans of 33 patients with traumatic occipitoatlantal dislocation with 73% sensitivity for predicting the need for operative intervention [28,32]. In stable individuals, virtually no movement should occur between flexion and extension. Dynamic motion of 1 mm is a proposed cutoff for pathologic movement based on a small series of patients with weakness and mechanical neck pain found to have atlanto-occipital translation of 2 and 5 mm between flexion and extension views [8,33]. In comparison, 20 adult controls had <1 mm horizontal translation on dynamic imaging. Pathological atlanto-occipital motion is often clearly above the 1 mm cutoff; however, this is not always true, and the small cutoff of 1 mm can be difficult to reliably observe [34].

Grabb, mapstone, and oakes measurement

The Grabb, Mapstone, and Oakes measurement characterizes the extent of basilar invagination and thus potential VBSC [22,35]. Denoted pB-C2, this measurement is calculated as the interval from the ventral dural edge perpendicular to the line drawn from the basion to the posteroinferior C2 vertebra (Fig. 1C). In a study of 40 pediatric and young adult patients with CM-1, the pB-C2 was found to correlate with the subjective grade of VBSC, with higher values associated with abnormal eye movements and other neurological abnormalities. All patients with a pB-C2 <9 mm were capable of undergoing treatment with posterior fossa decompression alone, regardless of subjective VBSC. However, some patients with a pB-C2 above 9 mm had neurological worsening after decompression, suggesting underlying instability rather than static compression. Reduction of VBSC decompression may be warranted in such patients [35].

Positional MRI

CCI symptoms are often positional, exacerbated by sitting, standing, or activity and alleviated when lying down. "Functional" or flexion–extension dynamic studies are useful in exploring these positional symptoms [36]. Upright or positional MRI (pMRI) allows assessment of biomechanical changes associated with physiologic weight-loading and normal CCJ motion. In both symptomatic and asymptomatic patients, studies have shown physiological and kinematic changes in the cervical spine when moving from a neutral position to extreme flexion or extension [37–42]. A study by Milhorat et al. of patients with CM and EDS demonstrated an increase in ligamentous laxity and instability on radiographs taken in the upright versus supine position; however, the utility of pMRI was not assessed [43]. Despite the academic value of pMRI, there is insufficient high-quality evidence to suggest that pMRI adds a clinical benefit to the diagnosis and management of CCI over traditional imaging modalities. A literature search that assessed publications from 1998 to 2014 reviewed the diagnostic utility of pMRI in CCI and EDS [44]. Their search identified 1100 studies for abstract review and 69 for full-text review; however, no studies directly compared the utility of pMRI to other modalities in the management of spinal or CCJ abnormalities in EDS. Additionally, no studies explored the diagnostic utility of pMRI in patients with symptomatic CCI.

Additional morphometric variables

In a large prospective review of 2,813 patients with CM-1, Milhorat et al. examined the incidence and morphometry of EDS and other hereditary CTDs [43]. Of the 357 patients with a hereditary CTD, 250 had EDS and 71 had overlapping characteristics for multiple CTDs. The authors analyzed recumbent and upright measurements of traditional morphometric variables, such as the atlantodental interval (ADI), CXA, and basion-dens interval, as well as newer morphometric variables, including the basion-atlas interval, dens-atlas interval, clival-atlas angle, and atlas-axis angle. They compared these values amongst the CM-1 cohort with hereditary CTD, CM-1 cohort without hereditary CTD, and a control group. Notably, CM-1 patients with hereditary CTD had a significantly larger basion-atlas interval (3.0 mm) and smaller basion-dens interval (3.6 mm), CXA (10.8°), clivus-atlas angle (5.8°), and atlas-axis angle (5.3°) in the upright position. These changes were reducible by cervical traction or returning to the recumbent position. The hereditary CTD subgroup also had a significantly higher incidence of lower brainstem symptoms and an increased risk of retro-odontoid pannus (> 3.0 mm) [45]. This pannus has been associated with chronic atlantoaxial subluxation [46], nonunion odontoid fractures [47], os odontoideum [48], and other metabolic and autoimmune conditions [49–52]. Hereditary CTD was also associated with a higher incidence of basilar invagination (71% vs. 11%). Morphometric measurements for the control group were not significantly different from those of CM-1 patients without hereditary CTD. Morphometric changes in this cohort therefore support the hypothesis that occipitoatlantal and

atlantoaxial joint hypermobility contributes to retro-odontoid pannus formation and basilar impression.

Differentiating CCI from hypermobility

The term "instability" has been criticized as inaccurate and unnecessarily alarming in the context of patients with EDS, and the hypermobility seen in EDS should be clearly differentiated from the instability seen in patients with traumatic or inflammatory arthropathies [18]. The distinction between CCI and hypermobility is critical, as CCI requires urgent stabilization, whereas transient neurological symptoms associated with hypermobility do not warrant aggressive surgical treatment [18]. Illustratively, Halko et al. demonstrated in a study of 26 patients with Type IV EDS that only 2 patients (8%) had atlantoaxial subluxation as indicated by the ADI on flexion–extension radiographs [53]. Grahame et al. reported consensus findings from a multi-specialty conference aimed at differentiating "benign hypermobility" from "pathological hyperextensibility" of the CCJ ligaments, or CCI [54]. They concluded that a radiological diagnosis of CCI, basilar invagination, or VBSC on dynamic imaging should be corroborated by clinical findings, and that neurosurgical intervention should be considered only when both radiographic and clinical findings indicate instability. Although this consensus was not based on patient data, the stakeholders' opinion reflects the importance of careful deliberation and investigation before surgical intervention for a diagnosis of instability in EDS patients.

However, distinguishing hypermobility from CCI is complicated by overlapping symptoms, including pain and transient neurological deficits [18]. Klinge et al. studied 8 patients with EDS but without CCI on magnetic resonance imaging (MRI). Ultrasound revealed that patients with EDS had increased spinal cord pulsation and abnormal movement at the CCJ. Additionally, myodural bridges collected intraoperatively and viewed under transmission electron microscopy demonstrated fibril disruptions leading to increased laxity. They argue that the irregular motion of the spinal cord caused by these disrupted myodural bridges may contribute to chronic neck pain and neurological symptoms in EDS, even in the absence of radiographic instability [55].

Identification of CCI in EDS patients remains challenging. A dearth of experimental models limits our understanding of the biomechanics of spinal stability in EDS [44]. The clinical data supporting proposed diagnostic criteria for CCI remain limited and the proportion of EDS patients with spinal or CCJ abnormalities is unclear [44]. Consequently, the morphometric variables proposed to diagnose CCI in the literature are based primarily on expert opinions, consensus criteria, and observational studies.

Management of CCI in patients with EDS

Management of clinically significant CCI is often based on symptom acuity, symptom severity, or both [4,56,57]. Individual anatomical variations also impact treatment, with surgery in children with CTDs being particularly challenging due to features such as aberrant vertebral artery course or dysmorphic osseous features [9,15]. The first-line therapy should consist of conservative management using a cervical orthosis and physical therapy. Patients should be advised to refrain from activities that worsen symptoms [9]. Some authors have referred patients for a trial of a rigid orthosis with cervical spine immobilization for 4–6 weeks to see if symptoms improve [58]. Progression of symptoms or failure of conservative treatment to improve symptoms are possible indications for surgical intervention (Table 1).

Surgical management

The decision-making for surgical intervention must consider several critical factors, including (1) anatomical variations inherent to the patient's age, condition, or prior surgeries; (2) necessity and feasibility of reducing deformity; (3) need for decompression; (4) cost–benefit calculus of preserving stability at the expense of range of motion; and (5) techniques available to ensure solid bony arthrodesis. Furthermore, hypermobility patients undergoing OCF are at increased risk for adjacent segment disease, rendering the choice of the lower-instrumented level particularly important [59]. Fusion can result in up to 50% loss of rotation and may limit future growth potential in pediatric populations [6,60–62]. Common perioperative complications include instrumentation failure and pseudoarthrosis, cerebrospinal fluid leak, subdural hematoma, infection, malpositioned screws, and vertebral artery injury [61,63–65].

Internal occipitocervical fixation is performed to immobilize the associated joints, reduce the CXA, relieve neurological compromise, and correct or improve alignment [1,4,62]. OCF can be achieved via a posterior approach or combined anterior/posterior approaches, and anterior approaches alone are seldom used for CTDs [56,66]. Rigid screw and plate fixation is generally preferred compared with semi-rigid fixation with wires and cables due to biomechanical superiority and improved long-term stability and bony fusion [1,4,61].

Fixation across the CCJ requires a strong cranial anchor, usually an occipital plate, connected by rods to the atlas, axis, or subaxial fixation points, often at the lateral masses. Care must be taken to avoid inadvertent injury to the torcula or venous sinuses [67]. Henderson et al. presented a single-surgeon consecutive series of 22 patients with hereditary CTD who underwent occiput-C2 open reduction with internal fixation for cervicomedullary syndrome [11]. They defined several criteria for surgical intervention, including severe disabling headache or neck pain, neurological deficits, failed conservative treatment, and radiological findings including CCI. Although not all had EDS, they recommend adopting the same criteria for patients with EDS. At 5-year follow-up, a 100% satisfaction rate was reported along with improvement in vertigo (92%), balance (82%), dizziness

Table
Summary of studies describing surgical management of CCI in EDS

Author, y	N	Mean age	Preop parameters	Postop parameters	Outcomes	Complications
Ahmed, 2013 [69]	2	30	NS	NS	OCF is associated with improvement in symptoms including resolution of headaches but also several postoperative complications. Careful management can help improve symptoms.	Upper airway obstruction from fusion in flexion alignment requiring fixation revision, intrusion of occipital screws into intracranial space, intrusion of C2 screws into spinal canal and neural foramen. Other complications discussed for non-EDS patients.
Alalade, 2019 [68]	1	10	CXA: 115 pB-C2: 18.2	NS	Combined approach using an endoscopic endonasal odontoidectomy and posterior decompression with fusion surgery is safe and effective in improving symptoms.	Transient dysphagia that resolved with conservative treatment. A non-EDS patient aspirated after extubation and required reintubation
Felbaum, 2015 [64]	2	12.5	CXA: 128	CXA: 151	Improvement in headaches, tremor, dizziness, gait after OCF in patients with a prior craniectomy defect.	No perioperative or hardware complications
Henderson, 2019 [11]	20	24	CXA: 127 pB-C2: 9.1 BAI: 4.9	CXA: 148 pB-C2: 6.7 BAI: 0.9	Craniocervical fusion improved CXA, pB-C2 and BAI improved to normal values, neurological deficits improved.	Intraoperative transfusion, superficial wound infections, pain from rib harvests, worsening of neurological deficits
Spiessberger, 2020 [58]	26	31.9	CXA: 131 pB-C2: 8.6	CXA: 145 pB-C2: 5.6	Both occipital bone and occipital condyle fixation techniques can improve CXA and pB-C2.	Asymptomatic vertebral artery occlusion, pseudomeningocele, transient weakness
Zhao, 2022 [80]	12	38	CXA: 139	CXA: 154	Instability can arise as a delayed complication after surgical treatment of CM-1 in EDS patients and can be managed with OCF.	No perioperative or hardware complications

BAI, basion-axis interval; CXA, clivo-axial angle; N, number of EDS patients; NS, not specified; pB-C2,Grabb, Mapstone, and Oakes measurement

(70%), ambulation (69%), Karnofsky performance status, and a decrease in headaches. Neurological deficits improved, the CXA increased from an average of 127° to 147°, and the BAI normalized in all patients postoperatively. Similarly, Martinez-del-Campo et al. reported in a series of 120 patients undergoing OCF for radiographic instability that 91% of patients with preoperative neurological deficits improved after surgery, although their series included patients with traumatic causes of instability, tumors, and other systemic conditions [61].

An occipital plate fixation is not always achievable in patients requiring a posterior fossa craniectomy for suboccipital decompression to relieve symptoms from cervicomedullary syndrome and tonsillar descent [58]. The occipital condyles projecting from the lateral portion of the occipital bone can be used as an alternative cranial fixation point in patients with CCI and EDS where fixation to the occiput is not permissible. These surgeries can be technically challenging and preoperative imaging including computed tomography angiography should also be performed to assess the anatomy and neurovascular structures near the condyles [67]. Several techniques have been described in the literature to guide the trajectories and screw lengths [67]. Biomechanical analysis has illustrated similar stability with occipital condyle screws compared with plates, and both reduce range of motion by about 80% [56].

Spiessberger et al. compared radiographic outcomes in 26 patients with EDS who underwent OCF, divided evenly between a cohort of 13 patients with occipital plate fixation and 13 patients with occipital condyle screw fixation [58]. They note that the patient anatomy should be considered as placement of occipital condyle screws can be challenging in patients with small condyles. Notably, postoperative morphometric measurements were comparable between the 2 groups, with improvements in the pB-C2 (8.8 to 5.7 mm and 8.3 to 5.4 mm, respectively, in the plate and condyle cohorts) and CXA (128° to 143° and 132° to 148°, respectively, in the plate and condyle cohorts) noted among all patients. No permanent post-operative neurologic complications were noted; however, trends in neurological improvement were not assessed.

Other studies reporting outcomes after surgery for CCI in EDS comprise small case series. Alalade et al. reported a pediatric patient with EDS and CM-1 who presented with suboccipital pain, dysphagia, dizziness, and myelopathy concerning for basilar invagination [68]. Initial CXA was 115˚ and the pB-C2 was 18.2 mm with radiologic evidence of VBSC. The patient underwent OCF from the occiput to C3 followed by endonasal endoscopic odontoidectomy. The postoperative course was complicated by transient dysphagia, but the patient improved from a modified Rankin Scale score of 3 preoperatively to 2 at 17 months follow-up. Felbaum et al. reported their experience with OCF in 3 pediatric patients, including 2 with EDS and a history of suboccipital craniectomies for CM-1, using an "inside-out" technique that involves creating 2 paramedian troughs in the suboccipital bone, allowing for introduction of a washer/bolt construct in the epidural space under the occipital bone functioning as an anchor for cranial fixation [64]. Following OCF, symptoms improved dramatically in both patients, with the CXA improving from 128˚ to 153˚ in one patient (Fig. 2) and 128˚ to 148˚ in the second patient.

Additionally, Ahmed and Menezes presented a series of patients with postoperative complications after occipitocervical instrumentation, including 2 patients with EDS [69]. One patient with headaches, nausea, and vertigo underwent OCF from the occiput-C3 with autologous rib graft, but experienced severe upper airway obstruction postoperatively with 2 failed extubation attempts. Radiographs demonstrated that fixation had been performed in a flexed position, and construct revision resulted in improvement of the obstruction and resolution of headaches. The second patient had previously undergone posterior fossa decompression and posterior OCF, and presented with debilitating headaches, occipital tenderness, and severe pain with cervical movement. CT of the CCJ revealed intracranial intrusion of the occipital screws and violation of the spinal canal and neural foramen by the C2 screws. The patient reported dramatic pain relief and dynamic imaging showed stable occipitocervical fusion following removal of cement and instrumentation.

Guidelines

Although no comprehensive clinical or radiographic algorithms exist for diagnosis and management of spinal instability in persons with EDS, several recommendations can be offered. A joint international conference of stakeholders suggested that hereditary CTDs, including EDS, are characterized by ligamentous incompetence, which may result in radiographic evidence of instability, basilar invagination, or VBSC in a small group of patients. They recommend dynamic imaging, including flexion–extension MRI and flexion–extension or rotational CT, and recording well-established mormophetric parameters of instability. Imaging should be followed by a neurosurgical evaluation in the clinic, and patients with both radiographic and clinical findings should be considered for craniocervical reduction, stabilization, and fusion [54]. A systematic review by Lohkamp et al. recommended using the CXA, BAI, pB-C2 measurements, and the angular displacement of C1 to C2 in the workup of CCI in EDS patients [70].

White's definition of instability requires mechanical instability that threatens neurologic function [5]. Although patients with radiographic and clinical evidence of instability are clear candidates for surgical intervention, others are referred to spine surgeons for abnormal radiographic CCJ metrics that are inappropriately identified as the primary generator of chronic headache or neck pain [18]. The published criteria for traumatic spinal instability in non-hereditary CTD patients is often used to diagnose "radiographic instability" in EDS patients [70]. However, the inherent hypermobility in EDS implies a different threshold for

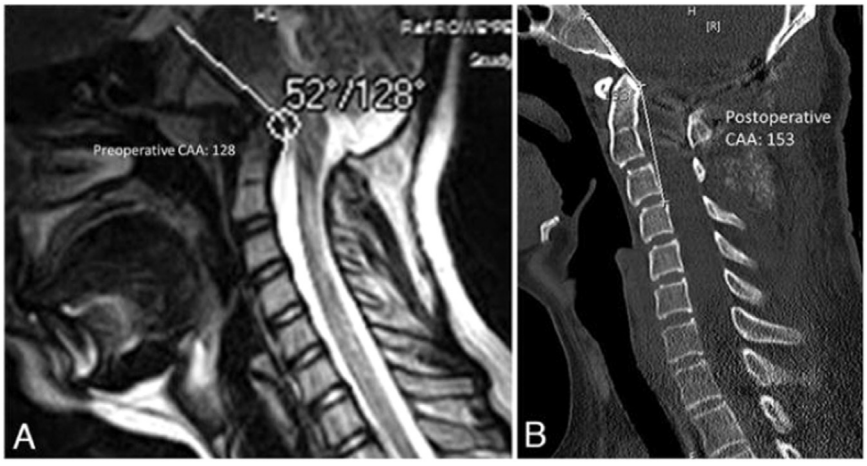

Fig. 2. Fusion from the occiput to C2 in a 14-year-old boy with EDS and a craniectomy defect for Chiari Type I malformation illustrating changes in the clivo-axial angle. A) Preoperative MR image demonstrating an angle of 128˚. B) Post-operative CT scan illustrates an angle of 153˚, within the physiological range of individuals without instability. *Obtained permission from Figure 3 in Felbaum D, Spitz S, Sandhu FA. Correction of clivoaxial angle deformity in the setting of suboccipital craniectomy: technical note.* J Neurosurg Spine. *2015;23:8–15.*

instability compared with the general population [18,70]. Ultimately, there is insufficient data comparing symptomatic and asymptomatic EDS patients to define such cutoffs, which may cause confusion as patients worry about imminent instability or VBSC in the absence of corroborating evidence on dynamic/positional MRI.

Contrasting instability in EDS and RA can help illustrate the unique management of hereditary CTDs and help refine criteria for diagnosis. Cervical spine disease is the second most common manifestation of RA, with approximately 15% of patients developing instability within 3 years of onset [71,72]. Primary indications for OCF in RA include neurologic compromise, vertebrobasilar insufficiency, or radiographic evidence of cranial settling with VBSC or atlantoaxial subluxation with posterior ADI <13 mm [73,74]. Neurological deficits are common and present in over 75% of patients [75]. Pellicci et al. demonstrated that 80% of patients with RA who had radiographic subluxation or instability progress within 5 years [76]. CCI in RA is similarly thought to arise from ligamentous laxity. Autoantibodies invade the synovium of joints, triggering a robust inflammatory response that destroys CCJ articular cartilage, weakens ligaments, and erodes the dens, generating a pannus [77] that can compress the spinal cord and cause myelopathy [45].

Despite the common factor of ligamentous laxity, the instability of RA and EDS is fundamentally different and cannot be assessed using the same conventional morphometric and radiometric measurements. In RA, the CCJ starts ostensibly normal and undergoes progressive destruction at onset of disease [78]. Therefore, as with traumatic CCI, comparison of CCJ metrics with normal individuals is appropriate. However, such a comparison is flawed in patients with EDS due to the benign hypermobility and ligamentous laxity associated with their disease [79]. Consequently, we posit that a separate set of values are needed to define stability and instability in EDS and other hereditary CTDs to differentiate hypermobility from pathological mobility and prevent patients from inappropriately undergoing surgery despite lacking true instability [18]. Therefore, there is a critical need for large-scale baseline morphometric measurements in EDS patients.

Future directions

Current EDS guidelines are based on expert opinions, anecdotal evidence, single-surgeon experiences, or extrapolation from trauma or autoimmune spine literature. A lack of large, validated clinical datasets hinders current diagnostic and management algorithms. Representative biomechanical or animal models for EDS are difficult to construct and the diagnosis remains largely clinical. Ultimately, more vigorous guidelines require a multicenter, prospectively maintained registry to collect data on symptomatology (pain with/without referable neurological symptoms), radiographic metrics, management protocols, and long-term outcomes for patients with EDS. Case-controlled studies using such a registry would assist in establishing the proper indications for surgical management.

Conclusion

CCI in EDS is a rare condition that requires thorough workup to distinguish the hypermobility associated with EDS from true clinical CCJ instability. OCF can help treat instability in patients with myelopathy; however, treatment sacrifices range of motion and can entail postoperative morbidity, particularly in younger patients. Therefore, it is critical to ensure that patients with EDS are not undergoing surgical treatment for hypermobility rather than instability. The CXA, BAI, and pB-C2 measurements can aid in the radiographic workup of instability. Larger multi-institutional databases are needed to determine the true impact of invasive surgical intervention on pain, function, and neurological outcomes.

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Supplementary materials

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