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RESEARCH REVIEW

Neurological and Spinal Manifestations of the Ehlers–Danlos Syndromes

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The Ehlers–Danlos syndromes (EDS) are a heterogeneous group of heritable connective tissue disorders characterized by joint hypermobility, skin extensibility, and tissue fragility. This communication briefly reports upon the neurological manifestations that arise including the weakness of the ligaments of the craniocervical junction and spine, early disc degeneration, and the weakness of the epineurium and perineurium surrounding peripheral nerves. Entrapment, deformation, and biophysical deformative stresses exerted upon the nervous system may alter gene expression, neuronal function and phenotypic expression. This report also discusses

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Conflicts of interest: The senior author is a consultant to LifeSpine, Inc., and is developing technology to improve craniocervical stabilization. The senior author holds patents on finite element analysis methodology that could be used to assess stress in the brainstem and upper spinal cord. The other authors declare they have no conflict of interest.

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increased prevalence of migraine, idiopathic intracranial hypertension, Tarlov cysts, tethered cord syndrome, and dystonia, where associations with EDS have been anecdotally reported, but where epidemiological evidence is not yet available. Chiari Malformation Type I (CMI) has been reported to be a comorbid condition to EDS, and may be complicated by craniocervical instability or basilar invagination. Motor delay, headache, and quadriparesis have been attributed to ligamentous laxity and instability at the atlanto-occipital and atlantoaxial joints, which may complicate all forms of EDS. Discopathy and early degenerative spondylotic disease manifest by spinal segmental instability and kyphosis, rendering EDS patients prone to mechanical pain, and myelopathy. Musculoskeletal pain starts early, is chronic and debilitating, and the neuromuscular disease of EDS manifests symptomatically with weakness, myalgia, easy fatigability, limited walking, reduction of vibration sense, and mild impairment of mobility and daily activities. Consensus criteria and clinical practice guidelines, based upon stronger epidemiological and pathophysiological evidence, are needed to refine diagnosis and treatment of the various neurological and spinal manifestations of EDS.

KEY WORDS: Ehlers–Danlos syndrome; headache; craniocervical instability; atlantoaxial instability; tethered cord syndrome

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INTRODUCTION

The Ehlers–Danlos syndromes (EDS) are a heterogeneous group of heritable connective tissue disorders characterized by joint hypermobility, skin extensibility, and tissue fragility. The significance of neurological findings of EDS have been recently proposed and reviewed [Voermans et al., 2009a; Savasta et al., 2011; Castori and Voermans, 2014]. The following article discusses the etiology and clinical findings related to neurological and spinal manifestations commonly observed, yet often poorly recognized, in EDS patients, and proposes treatment options and areas of research needed.

METHODS

On the basis of a large shared experience in the treatment of EDS, the authors were solicited to contribute a review of the neurological and spinal manifestations of EDS. The authors represent a working group within the International Consortium on the Ehlers–Danlos Syndromes. In preparation for the EDS International Symposium 2016, the authors formed subcommittees to research individual topics relating to EDS and its neurological presentations, and here present those findings in synthesized, topic-based fashion designed to assist a wider audience of medical practitioners in caring for EDS patients, and in advancing research needs for this population.

HEADACHE IN EHLERS–DANLOS SYNDROME

EDS patients commonly suffer a variety of headache types [Jacome, 1999; Martin and Neilson, 2014; Castori et al., 2015]. These include headaches due to migraines, muscle tension, intracranial hypertension, craniocervical instability, and cervical spine disorders, temporomandibular joint disease, carotid dissection, and other physical conditions. Though a patient may suffer status migrainosis, constant pain is less likely to represent a migrainous headache [Headache Classification Committee of the International Headache Society (IHS), 2013].

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Migraine in EDS

Epidemiology

Migraine, common in the general population, is more prevalent in women [Nappi and Nappi, 2012]. Migraine is also more prevalent among EDS which also has a female predilection [Bendik et al., 2011; Castori and Voermans, 2014; Castori et al., 2015]. Therefore, EDS may be considered a risk factor for migraine.

Etiology

Migraine often presents as a comorbid disorder with many other medical conditions [Schurks et al., 2009; Casucci et al., 2012; Pierangeli et al., 2012; Gelfand et al., 2013; van Hemert et al., 2014]. The final common pathway appears to be abnormal regulation of cerebral vasculature following a spread of depression of cortical electrical activity [Burstein et al., 2015; Ferrari et al., 2015].

Clinical and diagnostic findings

Defined as a primary headache disorder, with recurrent attacks of moderate or severe intensity, lasting 4–72 hr, migraine headaches are more often unilateral, pulsating, associated with nausea, photophobia, and phonophobia, which are disabling and worse with physical activity [Headache Classification Committee of the International Headache Society (IHS), 2013]. Migraine is usually preceded by a prodrome and followed by fatigue, nausea, and dizziness (postdrome). A careful history may

elucidate triggers such as foods, stress, weather changes, sleep changes, menses, seasonal allergies, and caffeine. Physical findings may include vertigo, hypersensitivity to pressure on certain muscles and tendons, elevated blood pressure, and heart murmur. Migraines may cause a benign episodic mydriasis. Findings may be suggestive of a stroke. Diagnostic testing should exclude sleep disorders [Kothari et al., 2000], menstrual cycle dysfunction including menopause [Nappi and Nappi, 2012; Ripa et al., 2015], and patent foramen ovale [Volman et al., 2013].

Treatment

Migraine therapies (e.g., botulinum toxin, triptans, caffeine, acupuncture, meditation) are legion, and testify to the diverse causes of migraine. Recognition that migraine patients suffer multiple pain disorders should prompt a holistic treatment strategy or combination therapies [Estemalik and Tepper, 2013; Kress et al., 2015].

Areas needing investigation

(1) Connection between migraine, EDS and mast cell activation syndrome (MCAS), and cardiac functional/structural defects, such as postural orthostatic tachycardia syndrome (POTS) and patent foramen ovale.
(2) Connection between migraine and diet in EDS.
(3) Prevalence and impact of migraine in all types of EDS.
(4) Treatment of migraine in EDS.
(5) Effect of other co-morbidities, medications, and nutrition in EDS related to migraine prevalence, severity, or treatment.

IDIOPATHIC INTRACRANIAL HYPERTENSION (IIH)

Epidemiology

IIH, or pseudotumor cerebri, is a poorly understood entity characterized by an increased intracranial pressure (ICP), headaches, visual disturbances and photophobia, and occasionally tinnitus, nausea, and vomiting. Affected patients may have objective changes in vision with 10% developing blindness [Corbett et al., 1982]. Female to male ratios range from 4:1 to 15:1, and obesity is an added risk factor [Radhakrishnan et al., 1993]. Anecdotal reports from large case series have suggested an association between EDS and IIH, but no such association has been formally reported in the biomedical literature.

Etiology

Hypotheses proposed for the etiology of IIH include excess cerebrospinal fluid (CSF) production, reduced CSF absorption, excessive brain water content, and increased cerebral venous pressure leading to reduced CSF reabsorption [Ball and Clarke, 2006]. Recent studies demonstrate that up to 93% of patients with IIH have focal venous sinus stenosis on MR venography, most commonly proximal to the transverse sigmoid sinuses junction, suggesting that venous abnormalities may play a role in the pathophysiology of IIH [Farb et al., 2003].

Clinical and Diagnostic Findings

The diagnosis of IIH requires symptoms of increased ICP. The visual disturbances are often associated with the finding of papilledema or visual field defects. The diagnosis is supported by increased ICP: >25 cm of H_2O in the obese population, or >20 cm H_2O in the non-obese population. There should be normal composition of CSF, thus, excluding inflammatory conditions, absence on MRI, or contrast-enhanced CT of hydrocephalus and of mass, structural, or vascular lesions, and no other cause of intracranial hypertension.

Treatment

Treatments include lifestyle modifications targeting weight loss including bariatric surgery, decreasing CSF production with acetazolamide, or serial lumbar punctures, CSF diversion with a ventriculo-peritoneal or lumbo-peritoneal shunt, optic nerve sheath fenestration, or subtemporal decompression. Stenting has emerged as an effective treatment for IIH in select patients with radiographic cerebral sinus stenosis and evidence of pressure gradients [Satti et al., 2015].

Areas Needing Investigation

(1) The epidemiology and etiology of pseudotumor cerebri in EDS.
(2) Longitudinal studies to assess the efficacy and risks of medical therapy, shunting, and stenting in the EDS population.

CHIARI I MALFORMATION (CMI)

Epidemiology

Chiari malformation Type I (CMI) has been reported as a comorbid condition in hypermobile EDS (hEDS) [Milhorat et al., 2007]. The precise incidence of the CMI and EDS association is unknown, but the female to male ratio is higher (9:1) in the CMI and EDS subgroup than in the general CMI population (3:1). The average age of onset tends to be younger in the CMI and EDS subgroup, when compared to the general CMI population.

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Etiology

CMI is a mesenchymal disorder affecting the hindbrain, in which a developmentally

small posterior fossa results in downward migration of the brainstem and cerebellar tonsils through the foramen magnum into the spinal canal [Batzdorf et al., 2015]. The herniation causes obstruction to the normal regional circulation of the cerebrospinal fluid (CSF) and compartmentalization of CSF circulation [Ellenbogen et al., 2000], which may result in suboccipital pressure headaches. Obstruction of the CSF circulation may result in empty sella syndrome, with flattening of the pituitary gland and resulting hormonal changes. A syrinx may form, which exerts a mass effect on the spinal cord, and rarely the brainstem [Kahn et al., 2015]. There is increasing recognition of CMI variants [Milhorat et al., 1999]. Some have suggested an association of tethered cord syndrome and CMI [Royo-Salvador, 1996].

The incidence, prevalence, and etiology of CMI and EDS occurring together are not fully understood. However, Milhorat et al. [2007, 2010] found a high prevalence of patients with hereditary disorders of connective tissue in their retrospective series of CMI post-decompression failures that needed further intervention, including craniocervical fusion and/or tethered cord release. While this may indicate a co-existence of these conditions, it does not provide evidence of a causal relationship, but suggests that EDS and other disorders of connective tissue should not be overlooked in CMI.

Clinical and Diagnostic Findings

The CMI is traditionally defined radiologically by 5 mm of tonsillar herniation through the foramen magnum, though others have suggested a herniation of 3 mm, or 7 mm. The behavior of CMI is often unrelated to the size of the herniation, and CMI can be asymptomatic.

CM is best characterized by a tussive headache (worse with cough, strain, or yelling), dizziness, cerebellar findings—dysarthria, incoordination, imbalance, and unsteady gait—hearing and vestibular deficits. Romberg's sign, and deficits of cranial nerves. There is sometimes trigeminal neuralgia [Milhorat et al., 1999; Tubbs et al., 2011a; Yarbrough et al., 2011]. Brainstem findings, such as sleep apnea and dysautonomia, are often found in CM that are complicated by craniocervical instability or basilar invagination, the so-called "complex Chiari."

Treatment

There is no universally agreed upon surgical threshold for CMI, but surgery should be urgently performed in the presence of progressive neurological deficits, and expanding syringomyelia (Fig. 1) [Yarbrough et al., 2011].

The association of CMI and EDS is burdened by distinct management challenges, including craniocervical instability, and possibly an increased risk of CSF leaks. CMI may be asymptomatic (incidence unknown), or mildly symptomatic, so that surgical intervention may not be required [Novegno et al., 2008; Strahle et al., 2011]. Sporadic cases of spontaneous resolution of CMI

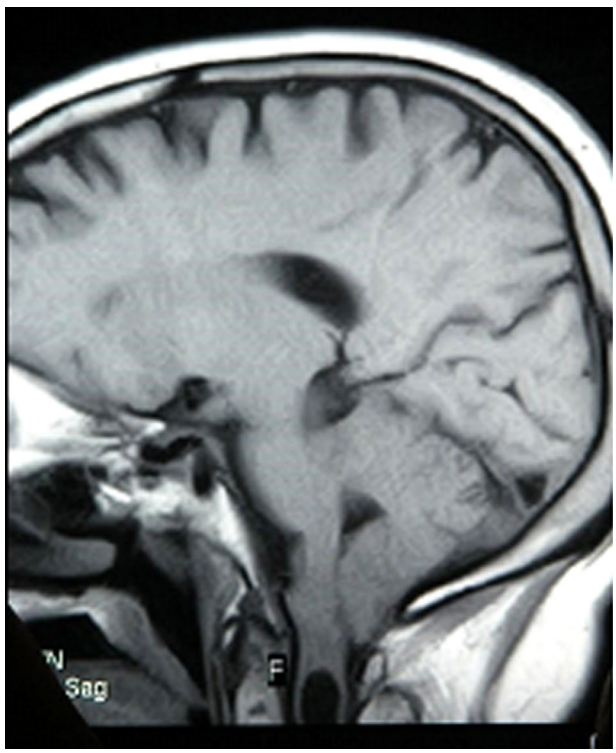

Figure 1. CMI with syrinx in the cervical spinal cord (sagittal view, T1 weighted MRI of the cervical spine).

have been described [Castillo and Wilson, 1995].

Areas Needing Investigation

(1) The incidence, prevalence, and etiology of CMI and its variants CM0 and CM 1.5 in the EDS population remains unclear and needs larger data registry
(2) The Complex Chiari malformation, though well described in the literature (see section on craniocervical instability), is not universally recognized among those who perform Chiari surgery. Prospective studies in EDS patients with Complex Chiari malformation are needed to compare outcomes following decompression alone versus those undergoing decompression with fusion/stabilization.

ATLANTOAXIAL INSTABILITY

Epidemiology

Atlantoaxial instability (AAI) is a potential complication of all forms of EDS. Motor delay [Jelsma et al., 2013], headache associated with "connective tissue pathological relaxation" and quadri-paresis have all been attributed to ligamentous laxity and instability at the atlantooccipital, and atlantoaxial joints [Nagashima et al., 1981; Halko et al., 1995].

Epidemiology

The epidemiology of AAI in hEDS is unknown. AAI was seen in two of three patients with vascular EDS [Halko et al., 1995]. A high risk of AAI is apparent in other disorders affecting connective tissue, including Down syndrome, Marfan syndrome, and rheumatoid arthritis [MacKenzie and Rankin, 2003; Hankinson and Anderson, 2010].

Etiology

A proclivity to ligamentous incompetence renders the atlanto-axial joint a higher risk for instability. The atlantoaxial junction (AAJ) is the most mobile joint of the body. The AAJ mechanical properties are determined by ligamentous structures, most prominent of which are the transverse and alar ligaments [Tubbs et al., 2011b].

Hypermobility of the AAJ is common in children, and over 40° of rotation may be observed in each direction, but in the adult there is substantially less than 40° of rotation [Zhang and Bai, 2007; Martin et al., 2010]. At 35° of rotation of C1 upon C2, there is stretching and kinking of the contralateral vertebral artery [Selecki, 1969]. At 45°, both vertebral arteries become occluded [Menezes and Traynelis, 2008].

Clinical and Diagnostic Findings

The diagnosis of AAI is predicated upon disabling neck pain or suboccipital pain, and

(1) history and clinical findings of cervical medullary syndrome, or syncopal (or pre-syncopal) episodes,
(2) demonstrable neurological findings, and
(3) radiological evidence of instability or compression of the neuroaxis.

Neck pain and suboccipital headache are the most common findings, with the caveats that headache is a common occurrence in EDS patients [Castori and Voermans, 2014]. There may be symptoms referable to the vertebral artery blood flow, including visual changes, as well as headache resulting from vertebral artery torsion. Syncopal and pre-syncopal events are frequent. Other symptoms include dizziness, nausea, sometimes facial pain, dysphagia, choking, and respiratory issues. Symptoms usually improve with a neck brace.

Neurological examination demonstrates tenderness over spinous process of C1 and C2, altered mechanics of neck rotation, hyperreflexia, dysdiadochokinesia, and hypoesthesia to pinprick. Weakness is not a constant feature of AAI.

A number of radiological features have been described, including rotation of C1 upon C2 $> 41°$ (as assessed by CT scan of C1-2) and retro-odontoid pannus on MRI [Fielding et al., 1978; Taniguchi et al., 2008]. The difficulty of recognizing rotary instability on standard X-ray, CT, and MRI images has resulted in failure to diagnose [Kothari et al., 2000].

Treatment

The first line of treatment should be neck brace, physical therapy, and avoidance of activities that provoke exacerbation of the AAI symptoms. If the non-operative treatment fails, fusion stabilization of C1/C2 is required. Incompetence of the alar ligament requires dorsal surgical fusion [Menendez and Wright, 2007]. Occiput to C1/C2 fusion should be considered in the presence of craniocervical instability, basilar invagination, or complex Chiari malformation.

Areas Needing Investigation

(1) The prevalence and natural history of AAI in the EDS population.
(2) The importance of dynamic imaging studies (such as CT with rotation of the cervical spine to extreme left and right, requires further validation to promote a generalized adoption of these studies to diagnose AAI, and to prompt greater availability of dynamic imaging facilities).
(3) Surgical outcomes for treatment of rotational instability and the long-term outcome in EDS.

CRANIOCERVICAL INSTABILITY

Epidemiology

Craniocervical instability (CCI) is recognized as a manifestation of ligamentous laxity in EDS [Nagashima et al., 1981; Milhorat et al., 2010]. Ligamentous laxity has been shown to result in neuraxial injury [Lindenburg and Freytag, 1970; Henderson et al., 1993; Menezes and Traynelis, 2008].

Etiology

CCI is a pathological condition in which ligamentous connections from the skull to the spine are incompetent. Motor delay, developmental coordination disorder, headaches secondary to spinal compression, clumsiness, and the relatively high rate of dyslexia and dyspraxia in the EDS population merit investigation as possible consequences of early onset degenerative changes resulting from ligamentous laxity upon the central nervous system [Nagashima et al., 1981; Adib et al., 2005]. The most prominent movement of the atlanto-occipital joint is flexion-extension; axial rotation is normally limited to <5 degrees of rotation [Dvorak et al., 1987].

There is increased recognition of mechanisms of neuronal injury that result from stretching, or deformative stress [Jafari et al., 1997; Maxwell et al., 1999; Shi and Whitebone, 2006]. The consequent formation of axon retraction balls is similar to that seen in diffuse axonal injury of the brain (Fig. 2) [Geddes et al., 2000; Henderson et al., 2005]. Stretching of neurons causes pathological calcium influx [Wolf et al., 2001], altered gene expression [Arundine et al., 2004], and apoptosis [Liu et al., 1997; Arundine et al., 2004].

Clinical and Diagnostic Findings

CCI-related symptoms result from deformation of the brainstem and upper spinal cord, traction on the vertebral artery, and possibly from the consequences of altered venous or CSF outflow from the cranium. CCI often occurs with basilar invagination or ventral brainstem compression, the findings of which are dominated by pyramidal and sensory changes: weakness of the limbs hyperreflexia and pathological reflexes (e.g., Babinski, Hoffman's sign, absence of the abdominal reflex), paresthesias, and a plethora of other symptoms—including sphincter problems, headache, neck pain, dizziness, vertigo, dyspnea, dysphonia, altered vision, and hearing, syncope, emesis, altered sexual function, altered menses, and gait changes [Caetano de Barros et al., 1968]. These signs, in aggregate, constitute the cervical medullary syndrome [Batzdorf et al., 2015], elements of which are commonly recorded among EDS patients [Celletti et al., 2012].

Three metrics may be useful in the identification of CCI and basilar invagination: the clivo-axial angle, the Harris measurement, and the Grabb, Mapstone, Oakes method [Batzdorf et al., 2015; NINDS Common Data Elements, 2016]. The Clivo-axial angle (CXA) is the angle formed between the posterior aspect of the lower clivus and the posterior axial line. The CXA has a normal range of 145° to 160°, but an angle of less than 135° is pathological [Henderson et al., 1993; Henderson et al., 2010a; Batzdorf et al., 2015]. Increasing kyphosis of clivo-axial angle (i.e., a more acute CXA) creates a fulcrum by which the odontoid deforms the brainstem [Menezes, 2012]. The medulla becomes kinked as the CXA becomes more kyphotic.

The second radiologic metric, the horizontal Harris measurement, is the distance from the basion to the posterior axial line (PAL) [Harris et al., 1994]. Instability is present when the basion to the PAL exceeds 12 mm. This measurement, used in conjunction with dynamic flexion and extension images of the cervical spine, can also be used to measure the dynamic translation between the basion and the odontoid [Batzdorf et al., 2015; NINDS Common Data Elements, 2016]. In the normal individual, there should be no measurable translatory movement

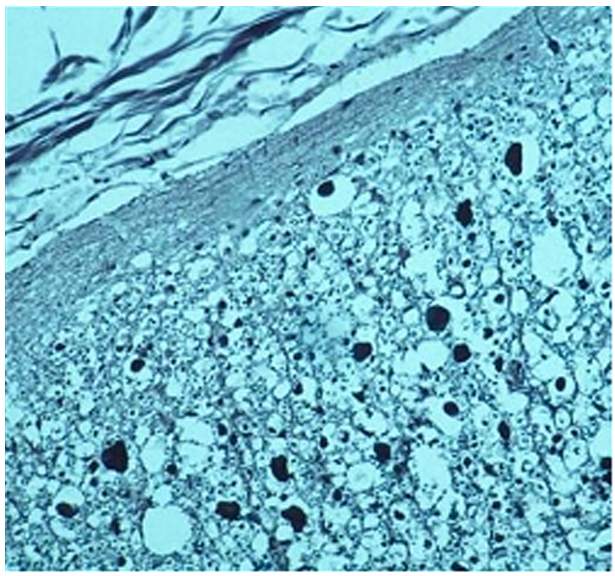

Figure 2. Axon retraction bulbs in the upper spinal cord, from cadaveric studies of subjects with basilar invagination (Microscopic photograph (×500), axial section of the dorsal column at the C2 level. Silver stain).

(sliding movement). Translation of greater than 1 mm between the basion and odontoid reflects craniovertebral instability, and may warrant stabilization (Fig. 3) [Wiesel and Rothman, 1979; White and Panjabi, 1990].

The third metric, the Grabb, Mapstone, and Oakes measurement predicts risk of ventral brainstem compression, and has been statistically correlated with clinical outcome [Grabb et al., 1999; Henderson et al., 2010b]. A measurement >9 mm suggests high risk of ventral brainstem compression [Grabb et al., 1999].

There is a relatively nascent recognition of the importance of dynamic imaging of the CCJ. For example, the brainstem may appear normal on routine magnetic resonance imaging in the supine position, but show pathological ventral brainstem compression in the flexion view sitting upright [Klimo Jr et al., 2008; Henderson et al., 2010b; Milhorat et al., 2010]. "Functional" dynamic studies in flexion and extension are important to determine whether there is pathological hypermobility at the craniocervical junction [Klekamp, 2012].

Treatment

Indications for surgery include severe headache, symptoms which constitute the cervical medullary syndrome, neurological deficits referable to the brainstem and upper spinal cord, radiological findings of CCI, and

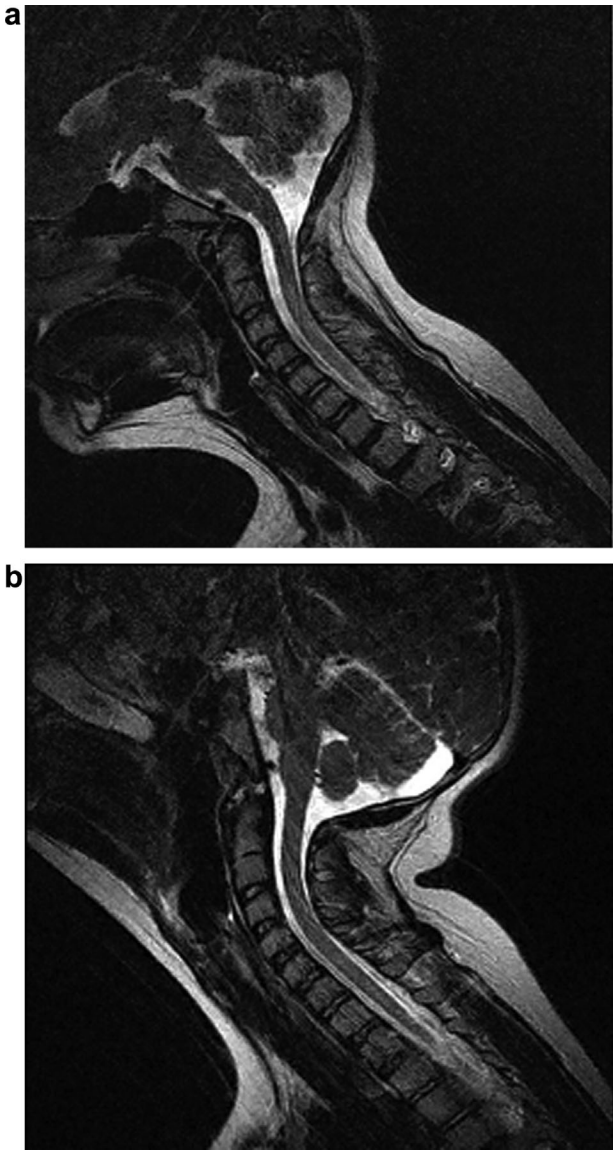

Figure 3. **a**: The craniocervical junction in flexion, showing a forward slide of the basion with respect to the odontoid (Sagittal view, T2 weighted MRI of the cervical spine in flexion). **b**: In extension, the basion lies along the posterior edge of the odontoid process, demonstrating a translation of 6 mm from flexion to extension (Sagittal view, T2 weighted MRI cervical spine).

failure of a reasonable course of non-operative therapy. Though there are no established criteria for treatment of CCI in EDS, there is abundant literature addressing the diagnosis of CCI [White and Panjabi, 1990; Harris et al., 1994; Batzdorf et al., 2015], and the treatment of CCI with craniocervical stabilization in various congenital or degenerative connective tissue disorders [Nagashima et al., 1981; Goel and Sharma, 2005; Henderson et al., 2010b; Milhorat et al., 2010; Tubbs et al., 2011a; Klekamp, 2012; Yoshizumi et al., 2014].

Areas Needing Investigation

(1) Prevalence and natural history of axial ligamentous instability in EDS.
(2) Validation of radiological metrics for determining CCI in the EDS population.
(3) Development of an international data registry using the NINDS Common Data Elements [2016] to facilitate therapeutic trials for CCI in EDS.

SEGMENTAL KYPHOSIS AND INSTABILITY

Epidemiology

The prevalence of cervical and thoracic segmental instability in the population of patients with hypermobility syndromes has not been well established. However, discopathy and early degenerative spondylotic disease in hEDS and classical type EDS is well established. EDS is characterized by segmental instability, kyphosis, and scoliosis. Spondylosis, defined by the presence of non-inflammatory disc degeneration, is usually preceded by mild segmental instability [Shedid and Benzel, 2007]. As a consequence of cervical and thoracic instability, and discopathy in EDS, there is loss of the normal cervical lordosis and an increasing kyphosis, rendering EDS patients prone to progressive myelopathy, and mechanical neck and chest pain.

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Etiology

Ligamentous laxity is an important determinant in the development of spinal instability other connective disorders such as rheumatoid arthritis, Down syndrome and osteogenesis imperfecta, but there have been no series to demonstrate this linkage in EDS. The importance of ligamentous laxity is increasingly appreciated among clinicians [Tredwell et al., 1990; Steilen et al., 2014].

The pathophysiology of segmental instability is well described: during flexion, there is deformation of the lateral and ventral columns of the spinal cord, directly related to the strain on the cord [Henderson et al., 2005; Shedid and Benzel, 2007]. Extension more often results in compression of the cord by buckling of the ligamentum flavum, resulting in myelopathic symptoms [Muhle et al., 1998]. The cervical spinal cord can be physiologically tethered in the sagittal plane, such that normal cord elongation in flexion is exaggerated by the kyphosis; this results in increased deformity and anatomic stretching of the cord. This "sagittal bowstring effect" underlies a physiological tethering effect, with resulting neurological deficits [Shedid and Benzel, 2007]. Others have recognized the importance of the dentate ligaments in applying stressors to the spinal cord, with the subsequent result of focal myelopathy [Cusick et al., 1977].

Clinical and Diagnostic Findings

Clinical findings include pain and disability, as well as sensory, motor, and reflex changes. Radiculo-myelopathy may manifest in an acute, subacute, or chronic manner as radicular and dermatomal or non-radicular myelopathic hypoesthesia, hyperesthesia, or paresthesia, and less often weakness. Over time, there may be ascending numbness, spasticity, Lhermitte's sign, and eventually leg weakness, altered gait, clumsiness, and long tract findings. There is often marked tenderness to palpation over unstable motion segments.

Clinical differential diagnoses in the EDS population should be kept in mind: instability at the atlanto-occipital and atlantoaxial joints, shoulder, clavicular and rib subluxations, brachial plexopathy, vascular anomalies, dissection or venous insufficiency, peripheral neuropathy, multiple sclerosis, amyotrophic lateral sclerosis, myasthenia gravis, myelopathy due to drugs—such as statins, colchicine, steroids- vitamin deficiency, especially B12 and B3, mitochondrial dysfunction, stroke, and psychological disorders.

Though CT scans and MRI remain the standard for most practitioners, radiological findings do not always correlate well with clinical findings or surgical outcome [Arnasson et al., 1987]. Dynamic instability is unlikely to be demonstrated in a resting supine subject, and pathological instability will often become manifest only when the ligaments are placed under stress. Though not yet validated, dynamic MRI in the upright position subjects the vertebral spine to physiological loading, and can be performed in the flexed and extended positions to demonstrate instability (Fig. 4) [Milhorat et al., 2010; Klekamp, 2012].

White and Panjabi [1990] have defined the reference ranges for flexion, extension, lateral tilt, and rotation

at each level of the spine. Radiological findings of segmental instability may include evidence of spinal cord compression or deformity, hyper-angulation at one or more segmental levels (>11.5° angulation between adjacent vertebra, subluxation >3 mm), and the presence of pathological longitudinal stretching.

Treatment

Initial management includes neck bracing and physical therapy with therapists who are knowledgeable regarding ligamentous laxity including EDS, attainment of a good sagittal balance, and avoidance of certain activities. Rest will often improve symptoms. If symptoms are refractory to conservative management, fusion, and stabilization of unstable levels may be indicated.

The rate of adjacent segment degeneration (the tendency for increased degeneration of discs adjacent to fused motion segments) has not been determined in the EDS population, but should be considered in surgical planning;

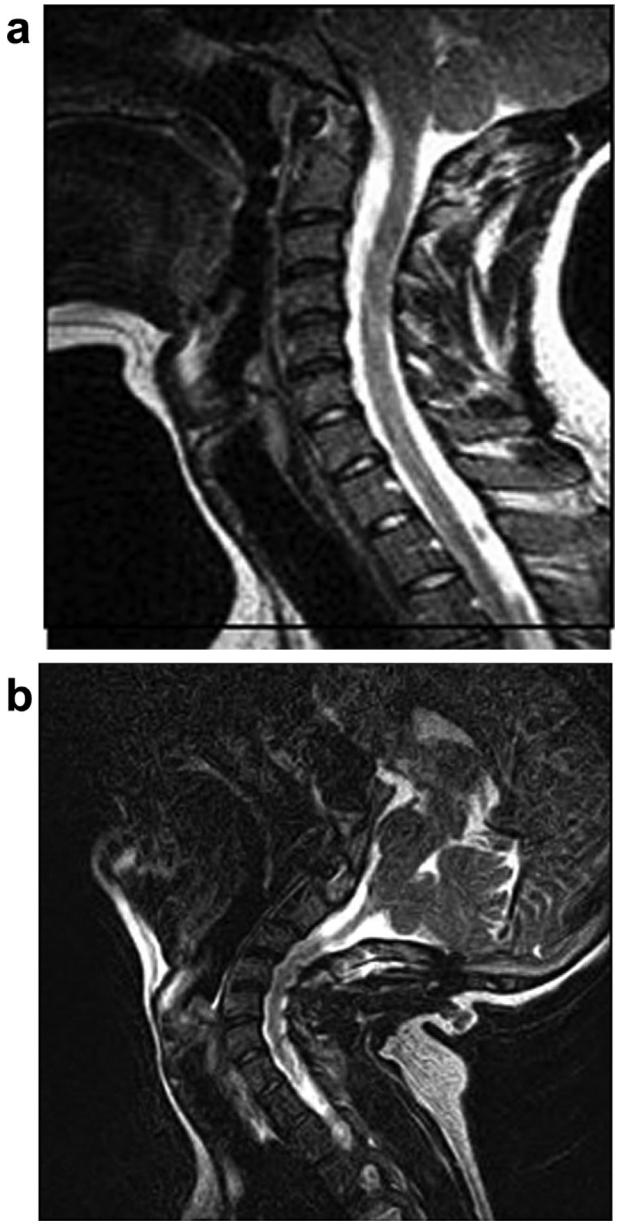

Figure 4. **a**: Segmental cervical instability, showing widespread degenerative disc disease characteristic of EDS-HT, but no spinal cord compression on neutral view (Sagittal view, T2 weighted MRI of the cervical spine in the neutral position). **b**: Dynamic instability evident upon extension of the neck, showing postero-listhesis of C4 on C5, causing spinal cord compression (MRI sagittal view of the cervical spine, T2 weighted).

motion-sparing technology may be an important option in this population, though there is yet no published literature in the EDS population.

Areas Needing Further Investigation

(1) Definition, prevalence and natural history of segmental instability in the EDS population.
(2) Clinical history of segmental instability after stabilization, including rates of adjacent segment degeneration in different types of EDS.
(3) Studies to improve diagnostic efficacy of segmental instability utilizing upright MRI.

TETHERED CORD SYNDROME

Tethered cord syndrome (TCS) in EDS is most often associated with a structurally abnormal filum terminale, and usually characterized by low back pain and the clinical triad of neurogenic bladder, lower extremity weakness and sensory loss, and musculoskeletal abnormalities.

Epidemiology

The incidence of the specific diagnosis of TCS is unclear, both within the general and EDS populations in the United States [Bui et al., 2007]. The prevalence of TCS in a diverse sample of Turkish school children was 0.1% [Bademci et al., 2006]. In a cohort of 2,987 consecutively evaluated patients with diagnoses of CMI or "low lying" cerebellar tonsils (LLCT, tonsillar descent 0–4 mm), Milhorat et al. [2009] found TCS, using a definition that allowed for normal position of the conus medullaris on MRI (i.e., at or above, the L1 vertebra), in 14% of the CMI patients they examined and in 63% of the LLCT cohort.

Etiology

The filum comprises a fibrous, collagenous, and elastic band that connects the conus medullaris with the dural sac at the S2 level. The filum contains neural, glial, and ependymal remnants that stem from embryonic spinal cord which begin to regress at 9–10 weeks of gestation [Jang et al., 2016]. The presence of fatty tissue, "nerve twigs" (dysplastic axons), fat and vascular lacunes, and suspicion of "congested" veins, are usually seen in the abnormal fila specimens obtained from patients with TCS [Thompson et al., 2014] Stretching of the spinal cord by the structurally abnormal filum is the presumed mechanism of TCS. Symptoms may become more apparent as a child grows. Forcible flexion and stretching is often deemed responsible for adult onset of TCS [Aufschnaiter et al., 2008]. Poor blood flow and oxidative stress in the spinal cord have also been implicated in animal models as mechanisms of neuronal injury [Yamada et al., 2007].

Clinical and Diagnostic Findings

TCS is characterized by aching/burning pain in the low back, legs and feet, and sensori-motor findings in lower extremities: weakness is common, with heaviness, stiffness, and tightness of legs and cramps; paresthesias in the pelvic area or legs and hypoesthesia to pinprick in the lumbar and sacral dermatomes is often observed. Findings are often asymmetric. A history of toe-walking may be elicited. Urological findings include urinary hesitancy, frequency, urgency, retention/incomplete emptying, nocturia, irregular urinary stream, sensory loss of the bladder, frequent urinary tract infections, and incontinence.

There is often enuresis into late childhood. There may be fecal incontinence, constipation, or sexual dysfunction. As TCS results in a combination of upper and lower motor neuron injury, there is often hyperreflexia in the lower extremities, but normal reflexes in the arms. The legs are usually weak, with normal upper extremity strength. Sensory loss is usually prominent in the lumbar and sacral dermatomes, but normal in the arms and trunk. Orthopedic deformities include scoliosis, kyphosis, functional ankle and foot deformities (ankle pronation with physical strain), and pes planus or pes cavus [Hoffman et al., 1976; Pang and Wilberger, 1982].

Urodynamic testing is important in the diagnosis of TCS. Neurogenic bladder manifestations may range from urinary retention and detrusor underactivity to urinary incontinence, overactivity of the detrusor, and sphincter dysfunction [Tu and Steinbok, 2013]. While formal urodynamic criteria have not been established for TCS, detrusor sphincter dysynergia, large post void residual, and very large bladder capacity (>800 ml) are good urodynamic indicators of a neurogenic bladder. Urodynamics can help to differentiate the neurogenic bladder of TCS from that due to diabetes or bladder obstruction from prostatic hypertrophy.

MRI of the cervical, thoracic, and lumbar spine is required to rule out other causes of leg weakness and low back pain, such as disc herniation, spondylolisthesis, stenosis, neoplasm, or intrinsic lesions of the spinal cord—such as multiple sclerosis or signs of trauma. The MRI may show low lying conus (below the mid L2 level), fatty infiltration, a stretched or thickened filum, a syrinx in the lower spinal cord, scoliosis or spina bifida occulta. The term "occult tethered cord" (OTCS) refers to where the MRI shows a normal position of the conus [Tu and Steinbok, 2013]. A large diameter of the filum terminale in axial T2 studies is a positive indicator that favors untethering in the presence of TCS [Fabiano et al., 2009].

Controversy exists over whether it is necessary to radiologically demonstrate a "low lying conus medullaris," that is, a conus ending at the lower L2 level or below. There has been the intuitive presumption that a low-lying conus represents a spinal cord under tension. However, this presumption has not been verified, and indeed, there are no epidemiological studies which allow the definition of a specific imaging finding to establish the diagnosis of TCS. Nor are there epidemiological studies in the normal population that demonstrate specific findings that

exclude TCS. On the other hand, there is a growing body of evidence that supports the clinical diagnosis of TCS with or without the radiological demonstration of a low-lying conus medullaris, which justifies surgical intervention when the clinical criteria are met [Tu and Steinbok, 2013].

Treatment of TCS

There is no standard technique in the surgical treatment of TCS. Generally, the lamina is removed, anywhere from L2 to S1, a durotomy is made, and electrical stimulation is used to confirm the absence of any nerve roots which may be associated with the filum. Finally, a microsurgical resection of the filum terminale (usually a 10 mm segment for pathology) is performed (Fig. 5). The filum tends to be taut, and to briskly retract upon sectioning. However, findings are variable, and there is no evidence to suggest that the intraoperative findings predict or correlate with the surgical outcome and severity of the TCS [Pang and Wilberger, 1982; Milhorat et al., 2009]. In some cases, it may be necessary to perform a lumbar stabilization across the motion segment in which the filum was sectioned. The resected filum should be sent for histopathological evaluation.

Areas Needing Research

(1) Prospectively and retrospectively evaluate specific clinical features and radiological metrics for predictive accuracy, to establish validated inclusion and exclusion criteria for future studies regarding TCS.
(2) Determine the incidence of TCS in EDS patients.
(3) Determine epidemiologically whether TCS is a co-morbid feature of CMI in EDS.
(4) Validate outcome measures by which to determine the surgical outcomes.
(5) Establish complication rates for TCS surgery in the EDS population.

DYSTONIAS AND OTHER MOVEMENT DISORDERS

Epidemiology

Movement disorders can be broadly divided into hyperkinetic disorders (too much movement) or hypokinetic movement occurring in the conscious state. The hyperkinetic movement disorders—including dystonia, tremor, chorea, myoclonus, and tic disorders—are observed in the EDS population according to anecdotal reports from large series of patients, but have not been documented in the peer-reviewed literature.

Etiology

Pain and trauma are frequent components of EDS, and there is a significant body of literature suggesting movement disorders may arise from extracranial trauma. Post-traumatic dystonia may develop in a limb following trauma to that limb [van Rooijen et al., 2011]. This may be one mechanism that establishes a link between EDS and movement disorders. However, while several of the authors have strong clinical suspicion of a connection, there are no published studies that confirm that movement disorders are a co-morbidity of hEDS [Rubio-Agusti et al., 2012].

While dystonia in joint hypermobility syndromes (JHS) have been observed, causality has not been demonstrated. In one large series, one third of patients with "fixed dystonia" were found to have JHS [Kassavetis et al., 2012]. The authors suggested that movement avoidance may have been adopted to avoid pain, and in time resulted in fixed dystonia. The etiology of the fixed dystonia has also been variously attributed to peripheral injury [van Rooijen et al., 2011], and psychogenic movement disorder [Hallett, 2016].

Clinical and Diagnostic Findings

Neurological evaluation and EEG to rule out seizure should be performed.

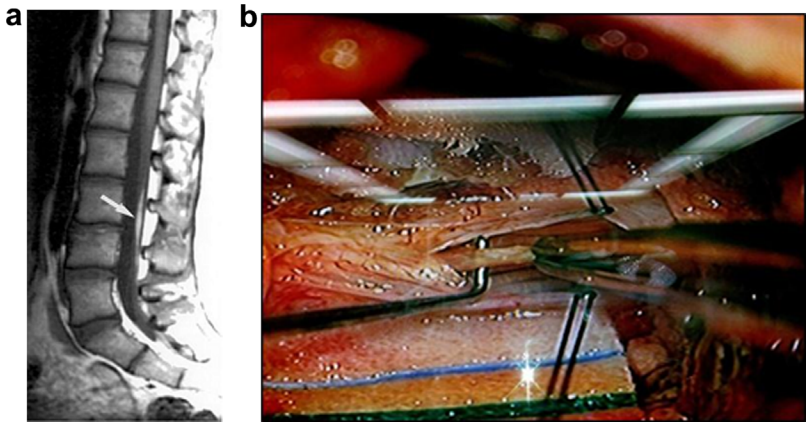

Figure 5. **a**: Tethered cord syndrome: conus at the normal level (L1), fatty filum suggestive of tethered cord syndrome (Sagittal view lumbar spine, T1 weighted MRI). **b**: Tethered cord syndrome: the thickened filum terminale at the L2 level, just before division. (Intraoperative photograph of the lumbar spine thecal sac and the durotomy).

The diagnosis of psychogenic movement disorder has been met with some skepticism [Palmer et al., 2016], but is distinguished from malingering, and thought to result from psychological causes [Hallett, 2016]; it is characterized by involuntary, disabling movements, abrupt in onset, a waxing/waning course, changes in the nature of the movement over time, worsening with stress, anxiety or depression, and improvement with distraction; they are difficult to diagnose and treat. Prognosis for improvement is better in patients with a shorter duration of illness [Lang, 2006].

Treatment

There is no established treatment algorithm for movement disorders in patients with EDS.

Areas Needing Research

(1) Establish studies to determine the epidemiology and etiology of movement disorders in EDS, and to demonstrate whether there is a comorbid relationship.
(2) Develop evidence-based treatment strategies for movement disorders in the EDS population.

NEUROMUSCULAR FEATURES OF EHLERS-DANLOS SYNDROME

Epidemiology

EDS, especially hEDS, is associated with high prevalence of myalgia, nocturnal muscle cramps involving the calves, hypotonia, progressive muscle weakness, poorly developed musculature, and scapular winging, which to some extent may be the result of avoidance of exercise due to hypermobility and instability of joints [Banerjee et al., 1988; Palmeri et al., 2003].

Musculoskeletal pain starts early, is chronic and debilitating [Voermans et al., 2010]. Neuromuscular disease manifests symptomatically with muscle weakness, myalgia, easy fatigability, and limited walking distance; physical findings include muscle weakness, reduction of vibration sense, and mild impairment of mobility and daily activities [Voermans et al., 2009b].

Musculoskeletal pain starts early, is chronic and debilitating. Neuromuscular disease manifests symptomatically with muscle weakness, myalgia, easy fatigability, and limited walking distance; physical findings include muscle weakness, reduction of vibration sense, and mild impairment of mobility and daily activities.

Brachial and/or lumbosacral plexus neuropathies and other compression mono-neuropathies are not uncommon in EDS [Voermans et al., 2006; van Rooijen et al., 2011]. The presence of radiculopathy or small-fiber neuropathy probably explains a higher prevalence of neuropathic symptoms (paresthesias/numbness in hands or feet) than registered on neurophysiological or ultrasound testing. There is a high prevalence of ulnar nerve luxation at the elbow detected on dynamic ultrasound [Granata et al., 2013].

Etiology

Some pathophysiologic studies are available on the relationship between tenascin-x(TNX) deficient EDS and neuromuscular complications. Human and murine studies suggest a correlation between TNX levels and degree of neuromuscular involvement, and a corresponding role of the extracellular matrix defect in muscle and peripheral nerve dysfunction in EDS [Huijing et al., 2010; Voermans et al., 2011]. However, TNX deficiency accounts for only a very small percentage of patients with hEDS. Reduced quantitative muscle function appears to be secondary to muscle dysfunction rather than reduced muscle mass [Rombaut et al., 2012]. Abnormal myo-tendinous junctions in the muscle belly [Penisson-Besnier et al., 2013], mild to moderate myopathy and/or neuropathy, and defects of the extracellular matrix of the connective tissue investing muscle and peripheral nerve may increase muscle dysfunction [Voermans et al., 2009b, 2012; Syx et al., 2015].

The pathophysiological mechanism of peripheral neuropathy in hEDS appears, in part, to result from abnormal stretching and pressure upon peripheral nerves that results from joint subluxation. The connective tissue of peripheral nerves might fail to resist excessive mechanical stress: increased vulnerability is linked to underlying genetic defects in TNXB, collagens I, III, or V deficient epi-, peri-, and endoneurium [Voermans et al., 2009b; Granata et al., 2013]. This defect might also relate to the occurrence of axonal polyneuropathy in various types of EDS [Muellbacher et al., 1998].

Abnormal extracellular matrix in generalized connective tissue structure suggests molecular overlap between inherited connective tissue disorders and certain congenital myopathies, awareness of which may be helpful in recognition of these rare disorders [Voermans et al., 2008; Donkervoort et al., 2015].

Clinical and Diagnostic Features

The approach to neuromuscular symptoms and signs, and helpful ancillary investigations has been thoroughly reviewed [Merrison and Hanna, 2009], and supplemented by the WUSTL database on neuromuscular disorders.

Treatment

A recent study on medical consumption and outcome reported the impact of pain upon daily functioning in hEDS.

Most patients (92%) used pain medications; 52% underwent physical therapy—including neuromuscular exercises, massage, and electrotherapy—of whom two thirds reported a positive outcome. The study concluded that the impaired functional status of hEDS patients strongly determined the high rate of treatment consumption, which underscores the importance of development of evidence-based guidelines for treatment [Rombaut et al., 2011]. There is increasing evidence that treatment should consist of a multidisciplinary program. One study demonstrated success combining physical therapy, cognitive behavioral therapy, and group therapy, followed by individual home exercises and weekly guidance by physiotherapist for three months, then readmission for reevaluation and further training advice. Patients reported improved performance of daily activities, muscle strength and endurance, reduced kinesiophobia, and increased participation in daily life [Bathen et al., 2013].

Areas Needing Research

(1) The contributions of the various causative factors to muscle dysfunction in EDS, including increased compliance of the series-elastic component of muscle tissue, failure of maximal voluntary muscle activation, and impaired proprioception.
(2) Clinical trials of physical training and cognitive behavioral therapy on muscle strength and endurance in EDS patients.
(3) The development of evidence-based guidelines to improve muscle strength.

TARLOV CYST SYNDROME

Epidemiology

Tarlov cysts are perineurial cysts that may impose pressure upon adjacent neural structures. Numerous small surgical series describe the spectrum of pathology, but there is significant confusion in the reported literature with other cystic structures: the sacral meningocele and dural ectasia. The sacral meningocele principally affects males, fills the sacrum, and typically involves all of the sacral roots. Dural ectasia may present with large intra-abdominal cysts associated with connective disorders [Nabors et al., 1988; Stern, 1988].

There is a general presumption that these cystic abnormalities, including Tarlov cysts, are incidental findings. However, the belief that all Tarlov cysts are asymptomatic has no support in the literature. An unpublished review at Johns Hopkins on 756 patients with symptomatic spinal cysts, found 18 with large sacral internal meningoceles with dramatic associated sacral erosion, of whom 16 were women with Marfan disease or EDS. The remainder had typical Tarlov cysts, with a female to male ratio of seven to one, usually on sacral nerve roots. A small number existed on the lumbar, thoracic or cervical roots. Delay in treatment resulted because most patients had been told that the cysts were asymptomatic and did not need to be treated, or that no satisfactory treatment existed, or that treatment was too dangerous to contemplate. Rarely, there may be massive dilatation of the lumbar and sacral thecal sac, with extensions of the subarachnoid space along nerve roots and into abdomen and pelvis.

Etiology

The finding of inflammatory cells in the walls of symptomatic Tarlov cysts [Voyadzis et al., 2001] begs comparison with the recent findings inflammatory cells in the fila terminale of EDS patients with TCS [Klinge, 2015].

Clinical and Diagnostic Findings

Tarlov cysts are a radiological diagnosis. The Tarlov cysts appear primarily in the sacrum, at the level of the root ganglia, causing erosion of the surrounding bone (Fig. 6). Cervical and thoracic Tarlov cysts may produce pain and neurological symptoms or deficits in the distribution of the involved nerve root, or myelopathic from an extradural or subarachnoid cyst in the high thoracic region, or symptomatic from a mediastinal cystic extension behind the trachea.

The most common syndrome, occurring in approximately 70% of symptomatic patients, is comprised of sacral pain, worse when sitting and standing, and improved when lying down; pain in the S2–S5 dermatomes in the pelvis and perineum, sciatica in the Sl and S2 dermatomes, and less commonly L5 root dermatome. Bowel and bladder dysfunction are common. One third of patients have bowel and bladder dysfunction, and sensory complaints related to nerve roots S2, S3, S4 without sciatica. A small group of patients have bowel and bladder dysfunction and sacral root sensory loss without pain.

Treatment

Of patients undergoing surgical obliteration of the Tarlov cysts, successful outcomes are reported in 80–88% of patients, with few complications [Voyadzis et al., 2001; Feigenbaum and Henderson, 2006]. Alternatively, patients may undergo aspiration of the cyst and injection of the cysts with fibrin glue, although the results are less satisfactory [Patel et al., 1997].

Areas Needing Research

(1) Determine the prevalence of Tarlov cysts in the general population and the hEDS and classic type EDS populations.
(2) Define the ratio of symptomatic versus asymptomatic patients, and the factors that appear to trigger pain.
(3) Compare the pathophysiology of Tarlov cysts in the general population versus the EDS population.
(4) A prospective randomized trial to compare treatments: surgical resection versus aspiration and injection of fibrin glue.
(5) Longitudinal studies of natural and clinical history of Tarlov cysts in EDS.
(6) Utility of urodynamic studies as opposed to patient report for symptoms of neurogenic bladder.

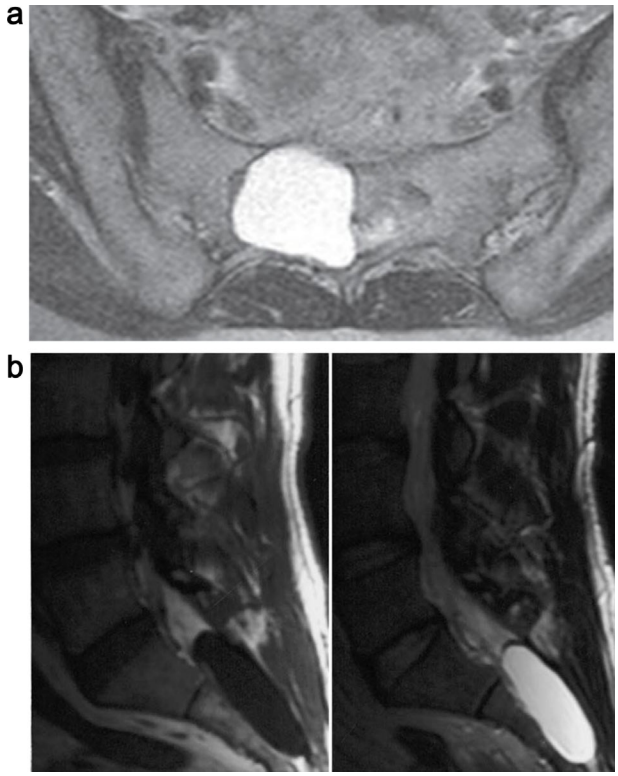

Figure 6. **a**: Tarlov cyst, with substantial bone erosion and compression of the right S2 nerve to the wall of the cyst in 9 o'clock position (T2 weighted MRI, axial view through sacrum). **b**: Large S2/S3 Tarlov cyst, T1 weighted view, Tarlov cyst on T2 weighted view (Sagittal MRI views through the sacrum).

CONCLUSION

Incompetent connective tissue results in lax ligaments within the axial skeleton, peripheral nerve sheaths, and possibly the architecture of the myoneural and muscular endplates. Ligamentous laxity of the axial skeleton in particular, subjects the central and radicular nervous system to entrapment, deformation, and biophysical deformative stresses. Biophysical stress is increasingly recognized in the alteration of gene expression, cellular function, and ultimately phenotypic expression. Clinical practice guidelines, based upon stronger epidemiological and pathophysiological evidence, are needed for the diagnosis and treatment of the various neurological and spinal manifestations of EDS.

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