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Diseased Filum Terminale as a Cause of Tethered Cord Syndrome in Ehlers-Danlos Syndrome: Histopathology, Biomechanics, Clinical Presentation, and Outcome of Filum Excision

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BACKGROUND: **Patients with hypermobile Ehlers-Danlos syndrome (hEDS), a heritable connective tissue disorder, present frequently with symptoms of tethered cord syndrome (TCS) but without a low-lying conus. Currently, surgical treatment of such cases is controversial. Because connective tissue disorder affects fibrous structures, we hypothesized that a diseased filum terminale (FT) might cause TCS in hEDS, justifying surgical transection for treatment.**

METHODS: **We investigated FT pathology, FT biomechanics, clinical presentation, and outcome following FT excision in 78 radiologically occult hEDS-TCS cases and for comparison in 38 typical TCS cases with low-lying conus and/or fatty FT infiltration but without hEDS.**

RESULTS: **In hEDS-TCS, electron microscopy revealed inherited collagen fibril abnormalities and acquired fibril damage. Biomechanical tension tests revealed elastic properties of the FT in both study groups, but they were impaired in the hEDS TCS. Follow-up examinations at 3 and 12 months after FT excision showed statistically significant improvement of urinary, bowel, and neurologic symptoms in both study groups; intergroup comparison revealed no differences in outcome except more pronounced neurologic improvement in the hEDS-TCS group.**

CONCLUSIONS: **Both morphologic findings and biomechanical tests indicate limited elastic properties of the FT in hEDS, which is no more able to dampen but still transmitting spine movement—related stretch forces. That mechanism exposes the conus medullaris to unphysiologic stretch forces, causing TCS, especially when considering the hypermobile spine in hEDS. This notion is supported by the observed clinical improvement following FT resection in hEDS-TCS cases without a low-lying conus.**

INTRODUCTION

Heritable connective tissue disorder (CTD) is a pathology presenting with a variety of clinical entities. Among them is hypermobile Ehlers-Danlos syndrome (hEDS), with a presumed prevalence of 1/5000[1] and physical hallmarks including joint and spine hypermobility[2,3] Clinically, patients often present with progressive back and leg pain, sensorimotor deficits in the lower extremities, and bladder and bowel dysfunction.[4,5]

The constellation of the above symptoms is well known as tethered cord syndrome (TCS). In clinically diagnosed TCS cases with radiographic evidence of a low-lying conus medullaris, the

Key words
- Biomechanical analysis
- Connective tissue disorder
- Ehlers-Danlos syndrome
- Filum terminale pathology
- Surgical outcome
- Tethered cord syndrome

Abbreviations and Acronyms
CTD: Connective tissue disorder
FT: Filum terminale
hEDS: hypermobile Ehlers-Danlos syndrome
MRI: Magnetic resonance imaging
RCT: Randomized clinical trial
TCS: Tethered cord syndrome
TEM: Transmission electron microscopy
UDS: Urodynamic study

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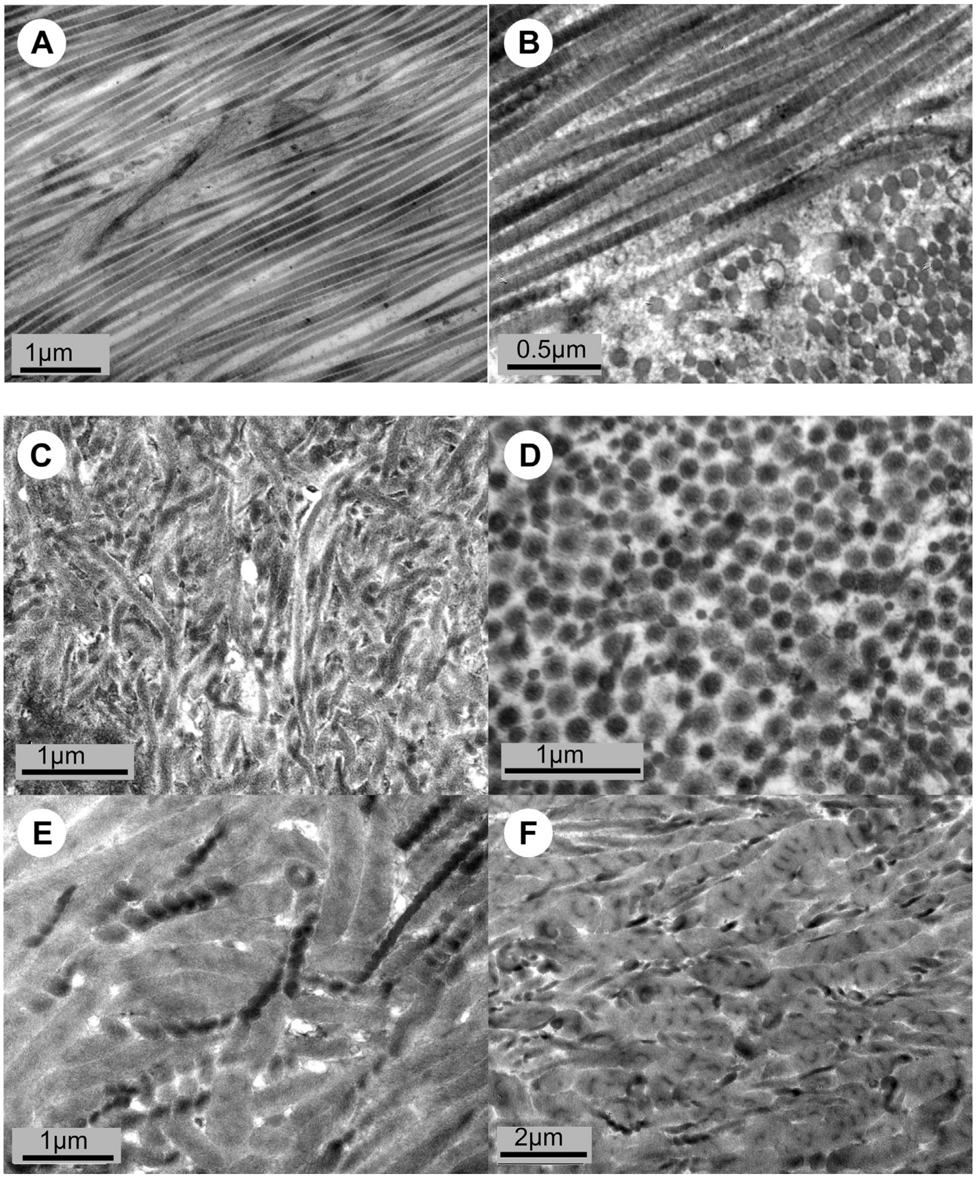

Figure 1. Transmission electron microscopy (TEM) of the filum terminale (FT) specimens without hypermobile Ehlers-Danlos syndrome (hEDS) comorbidity typically showed a regular cross-sectional and longitudinal arrangement of collagen fibrils (**A**). Higher magnification shows the physiologic D-period banding of the fibrils and a uniform fibril diameter, as well as regular distribution of the fibrils (**B**). TEM of hEDS specimens revealed findings consistent with both hereditary and acquired components of FT damage. As compared with part **A,** parts **C, E,** and **F** illustrate the loss of longitudinal alignment and appearance of irregular interwoven fibril structures, which has been recognized as pathology associated with hereditary connective tissue disorder.[17,18] As compared with part (**B**), parts **D, E,** and **F** show acquired damage indicating the mechanical overload of the FT.[19] (**D**) Swollen fibrils with varying diameter often display a halo, most likely indicating denatured collagen. (**E** and **F**) Collagen fibril microdamage in greater detail. The loss of the physiologic D-period banding is apparent in **E**. Dark spots posing as a "string of beads" indicate the kinking of fibrils representing local unwinding of fibrils occurring in response to a mechanical overload.[20,21] (**F**) Fibril swelling with aberrant, "zebra-like" D-period banding.

Table 1. Transmission Electron Microscopy Findings of the Filum Terminale

	hEDS-TCS (n = 78)	TCS (n = 10)	Chi-Square with Bonferroni Correction
Congenital collagen abnormalities			
Fibril disorganization	69.6%	10.0%	$P < 0.001$
Variation in fibril diameter in cross section	40.5%	11.1%	$P < 0.001$
Acquired collagen microdamage			
Kinking fibrils	63.3%	30.0%	$P < 0.05$
Loss of D-period banding	68.4%	30.0%	$P < 0.01$

The filum ultrastructure of the EDS-TCS and typical TCS cases was evaluated in longitudinal and cross sections. Markers of EDS collagen structural abnormalities such as fibril disorganization and variation in fibril diameter in cross section were assessed as well as markers of collagen microdamage such as kinking fibrils and loss of D-period banding.
hEDS, hypermobile Ehlers-Danlos syndrome; TCS, tethered cord syndrome.

surgical transection of the filum terminale (FT) is an established surgical intervention because the shortened FT is assumed to cause stretch-induced neuronal injury to the conus.[6] Patients presenting with TCS in the absence of low-lying conus have also been treated by FT transection.[7,8] Because those radiologically occult TCS cases cannot be objectively diagnosed and the underlying pathology is not known, the rationale for surgery has been questioned[9-12] and remains controversial.

Since we recently found distinct alterations of the collagen fibril architecture of the FT in horses with CTD,[13] we hypothesized that this pathology also exists in hEDS patients, causing radiographically occult TCS. Because comorbidity of TCS and CTD has never been investigated, we conducted a prospective study on the outcome of FT excision in hEDS-TCS patients and compared the results with typical TCS cases without hEDS but with radiographic evidence of low-lying conus and/or fatty infiltration of the FT. We report our clinical results and the pathology and biomechanics of FT specimens taken during surgery.

METHODS

Inclusion Criteria

From 2014 to 2018 our prospective study recruited 78 consecutive TCS cases with hEDS comorbidity but without low lying conus and was referred to as the "hEDS-TCS" group. The 38 consecutive TCS patients with low-lying conus and/or a thickened, fat-infiltrated FT without hEDS comorbidity was referred to as the "TCS" group. In both study groups, the diagnosis of TCS was based on clinical criteria established in the pediatric and adult population (i.e., bowel and bladder deficits, weakness and sensory deficits of the lower extremities, and a pain syndrome including lower back and extremity pain).[6,14,15]

The diagnosis of hEDS was confirmed by study-independent geneticists according to established diagnostic criteria.[3] The median age was 31.6 years (range 7.9−58.6) in the hEDS group and 36.4 years (range 6.5−69.2) in the TCS group. In both groups, only pediatric cases older than the age of 6 years were included to ensure a proper clinical assessment of symptoms. For inclusion, clinical symptoms were required to be progressive and resistant to conservative treatment for at least 6 months before surgery. Patients with myelomeningocele, split cord malformation, or other spinal abnormalities were excluded from both groups.

To exclude patients with nonneurogenic causes for bladder dysfunction, a urologic examination conducted by study-independent urologists was mandatory in hEDS-TCS and ordered at investigator's discretion in TCS. Preoperative urodynamic studies (UDSs) were available in 76 hEDS-TCS and 13 TCS cases. All patients with completed UDS were diagnosed with abnormal urinary function without identifiable organic causes. Frequent diagnoses were detrusor sphincter dyssynergia or detrusor pressures including stress urinary incontinence (53%); increased bladder capacity associated with incomplete emptying due to decreased sensation and impaired decreased EMG contractility associated with detrusor underactivity (22%); decreased bladder capacity (16%); and incomplete emptying with increased postvoid residual including stress urinary incontinence (9%).

The study protocol did not include postoperative UDS since we recognized ethical issues; a limited diagnostic power of this invasive procedure for the follow-up study of TCS surgery has been reported.[9]

A preoperative noncontrast standard magnetic resonance imaging (MRI) of the entire neuroaxis was conducted by study independent radiologists in both groups. In the TCS group the MRI revealed a low-lying conus at or below the L2/3 level ($n = 18$) and/or a thickened, fat-infiltrated FT ($n = 25$).

Clinical Visits

Three in-person study visits were conducted, 1 preoperative and 2 scheduled at 3 and 12 months after surgery. A comprehensive clinician-reported neurologic examination was conducted at the first and third visits but for tailoring of study resources not at the second visit. Subjective symptoms and adverse events were documented at each visit. Lumbar MRI was performed 6 months after surgery to assess the integrity of the surgical site. Clinical data were recorded by means of prospective clinician- and patient-reported assessments.[16] Only "moderate to severe" but not "none or mild" symptoms and findings were recorded and statistically analyzed in a binary fashion as present or absent.

Surgical Technique

All cases were surgically treated in a standardized fashion with intraoperative electromyographic neuromonitoring by a single neurosurgeon (P.K.). Surgery was performed through a lumbar interspinous approach 1 vertebral level below the conus. Following durotomy under microscopic magnification, a segment of at least 2 cm of the FT was excised. The dura was closed primarily and sealed with fibrin sealant (Tisseel, Baxter,

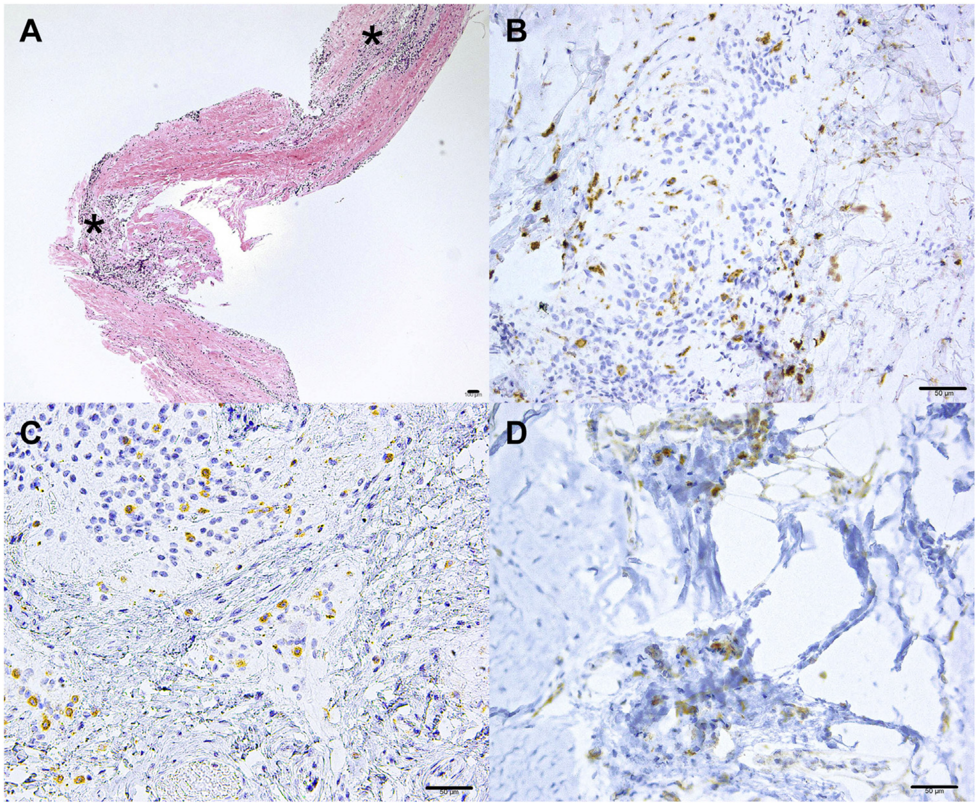

Figure 2. (**A**) Representative hematoxylin-eosin stain of the filum terminale at lower magnification showing regions of dense cellularity *(asterisks)*. Areas examined in hypermobile Ehlers-Danlos syndrome specimens with immunohistochemistry confirmed local inflammation. Common leucocyte marker CD45 (**B**), markers of microglial (CD68, **C**), and immunologically activated mast cells (CD117, **D**) were applied.

Deerfield, Illinois, USA) and a Duraform patch (Natus Medical Inc, Pleasanton, California, USA). Patients were subjected to a 24-hour bed rest post surgery.

Light Microscopy

FT samples from all patients were fixed in formalin and embedded in paraffin. Longitudinal 4-μm sections were prepared for routine hematoxylin-eosin stain. The FT of 19 consecutive hEDS-TCS cases were immunohistochemically stained for inflammatory cell types, applying CD45 for identification of lymphocytes, CD68 for microglia, and CD117 for mast cells.

Transmission Electron Microscopy

Transmission electron microscopy (TEM) of the FT was conducted in all hEDS-TCS and 10 consecutive TCS cases without hEDS. Specimens were fixed in glutaraldehyde and embedded in epon-araldite. Ultrathin sections (80 nm) were cut (Reichert-Jung Ultracut E) and poststained with uranyl acetate and lead citrate.

Biomechanics

Fresh FT specimens were obtained from TCS surgery in 2021 (8 hEDS-TCS and 10 TCS consecutive cases). The exact diameter of each sample was measured with calipers before testing. An MTS Bionix Tabletop Servohydraulic Test System (MTS, Eden Prairie, Minnesota, USA) equipped with a 125 N load cell was used to conduct tension tests. Samples were clamped in tension with a gauge length of 10 mm.

Stress (stretch force/cross-section area) was measured in response to increments of strain (relative elongation). A constant displacement rate of 0.03 mm/s was employed, and FT samples were stretched until 15% elongation was reached.

Statistics

Comparison of clinical presentation and TEM findings between groups was carried out using chi-square tests. For analysis of clinical outcome following surgery, the McNemar test was used for intragroup analysis and the chi-square test for intergroup analysis comparing typical TCS with hEDS-TCS cases. Biomechanical

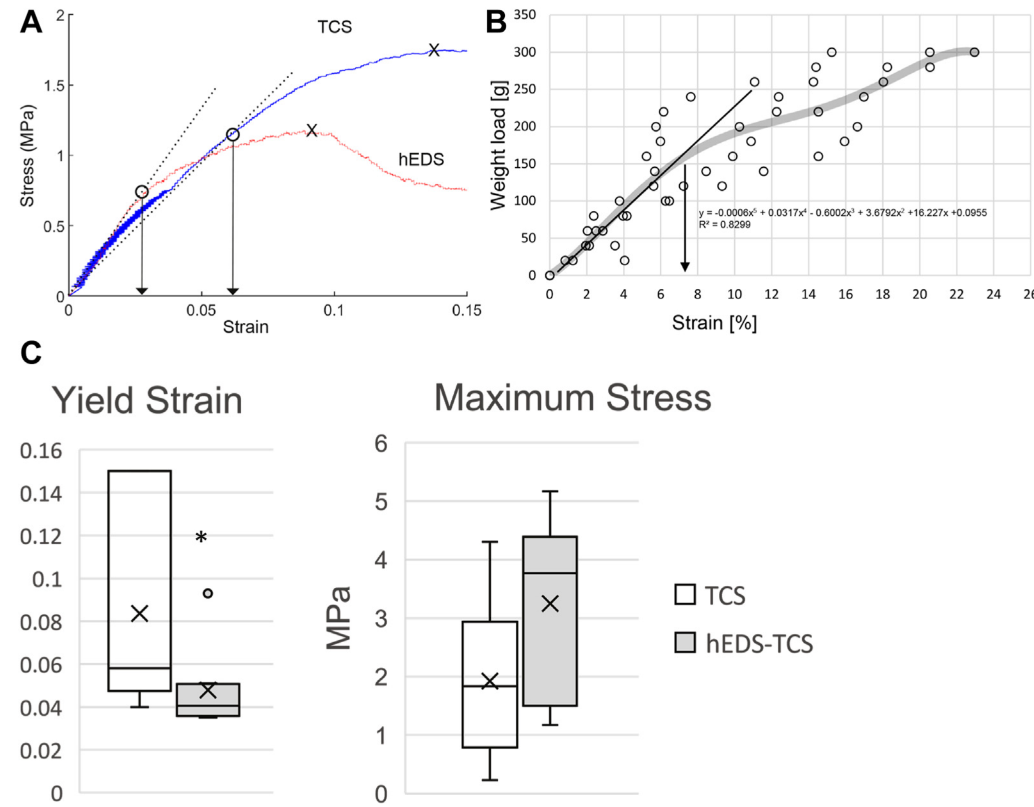

Figure 3. (**A**) Strain-stress curves of the human filum terminale comparing a hypermobile Ehlers-Danlos syndrome (hEDS)–tethered cord syndrome (TCS) sample with a typical TCS specimen. The point where the curve becomes nonlinear is circled. *Arrows* point to the yield strain (maximum elastic strain). X indicates the maximum stress. (**B**) Sampled biomechanical data from a previous study investigating 3 fresh human cadavers without history of CTD or TCS.[25] Strain is plotted against an increasing weight load. A fifth order polynomial regression curve *(MS Excel)* fits the data best ($R^2 = 0.83$). That fitted curve is quite like those of our TCS samples and indicates a yield strain of about 7%. (**C**) Boxplots of yield strain and maximum stress in the hEDS-TCS and typical TCS group. There is a considerable variance, but differences are statistically significant for the yield strain. The maximum stress was assessed up to a strain of 15% and was higher in the hEDS-TCS group, but this was not significant.

parameters between groups were tested using Mann-Whitney U tests. For all tests, $P < 0.05$ was taken to indicate statistical significance. All analyses were completed using R 4.0.3 (www.r-project.org).

Ethical Approval

Ethical approval for the study was obtained under Institutional Review Board protocols 787945, 1360957, 1107867, and 1694825 including informed consent from patients and/or their legal guardians.

RESULTS

Transmission Electron Microscopy

hEDS FT specimens showed structural collagen abnormalities such as fibril disorganization including abnormal fibril structures and variation in fibril diameter (Figure 1). In addition, we found signs of collagen fibril microdamage. The latter was indicated by kinking collagen fibrils and loss of D-period banding of the fibrils. The hEDS specimens differed statistically in all those criteria from the TCS group without hEDS (Table 1).

Immunohistochemistry

We found an inflammatory cell invasion in the hEDS specimens. CD45-positive leukocytes were observed in 16/19 cases (84%). Microglia were identified using CD68 in 15/19 cases (79%). CD117-positive mast cells were observed in 5/19 cases (26%). Figure 2 shows representative immunostainings that were captured in areas of higher cellularity within the FT specimen.

Biomechanics

The mechanical characteristics of the FT were investigated in analog-to-tension tests applied in muscle-tendon physiology.[22-24] Samples are stretched at a rate of 0.03 mm/s until 15%

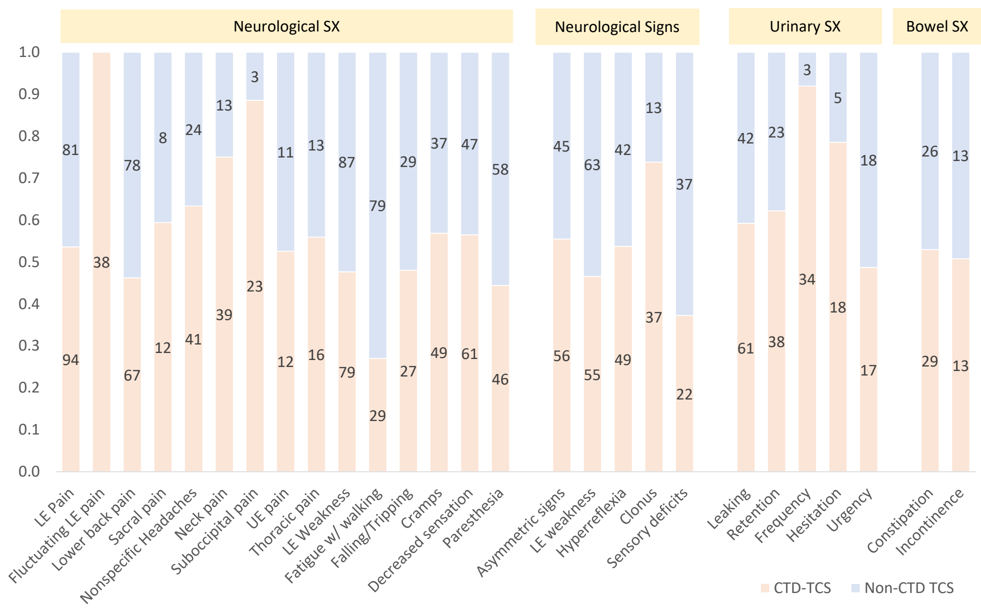

Figure 4. This stacked bar chart shows at the y-axis the relative proportion of cases presenting a specific symptom comparing the 2 study groups. The numbers within each bar indicate the percentage of cases presenting the specific symptoms within each of the 2 groups. SX, patient reported symptoms; signs, objective findings.

elongation was reached. Strain (relative elongation) and the related stress (stretch force/cross-section area) are plotted to obtain strain-stress curves. Such curves are highly nonlinear but initially show a proportional linear relationship between strain and stress. The point at which the curve becomes nonlinear and flattens marks the maximal elongation up to which elasticity is provided ("strain yield").

The strain yield was 8.4% ± 4.4% in typical TCS and 4.7% ± 1.9% in the hEDS-TCS group (mean ± SD, $P = 0.046$). The lower strain yield in hEDS indicates a limited range of elastic elongation.

With further elongation above the strain yield, high stress levels were maintained. Measured up to 15% strain, the maximum stress was 1.9 ± 1.3 MPa in the TCS and 3.3 ± 1.7 MPa in the hEDS-TCS group (mean ± SD, $P = 0.10$).

All biomechanical results are illustrated in Figure 3.

Clinical Presentation and Outcome

At the preoperative visit, study groups presented with a wide spectrum of urinary, bowel, and neurologic symptoms and findings. In the hEDS-TCS but not the TCS group, patients frequently reported lower-extremity pain to be fluctuant and even alternating between legs on day-by-day basis. Also, "pain all over the body" including headache and suboccipital and neck pain was dominant in hEDS cases. Figure 4 compares the proportion of clinical signs of both study groups and displays the frequency at which specific symptoms were observed within each group.

For outcome assessment, we analyzed the percentage of patients presenting at each visit with at least 1 "moderate to severe" bowel, bladder, or neurologic symptom or finding. That analysis reveals that bowel and bladder symptoms improved most following surgery, while at least 1 moderate-severe neurologic symptom was still present in many cases at the second and third visits. Comparing study groups, the clinical presentation overall was quite similar (Table 2). Chi-square testing revealed a better outcome in hEDS-TCS versus typical TCS cases in regards to the percentages of residual neurologic symptoms (46.7% vs. 72.4%, $P = 0.022$).

For within-group analysis of outcome, we used only those 59 hEDS-TCS and 26 TCS cases who completed both follow-up visits. We found that within each group, all diagnostic categories (urinary, bowel, neurologic) were significantly improved (Table 3, Figure 5).

Adverse Events

A temporary or permanent worsening of the clinical condition during the follow-up period was recorded in 10/78 hEDS and 5/38 TCS cases (12.8% vs. 13.9%). In the hEDS-TCS group, a surgical revision for a pseudomeningocele and a subsequent tethering of cauda structures were recorded. In the TCS group, 1 tethering of cauda structures and a filum terminale hemorrhage required surgical revision (Table 4).

DISCUSSION

The FT has been understood as an elastic structure protecting the conus medullaris against damaging stretch injury.[26,27] This has been previously supported for the human FT by just a single biomechanical cadaver study.[25] Our data provide the first strong

Table 2. Intergroup Comparison of Clinical Presentation Between Hypermobile Ehlers-Danlos Syndrome (hEDS-TCS) and Tethered Cord Syndrome (TCS) Group

	1st Visit				2nd Visit				3rd Visit			
Group	**Bowel**	**Urinary**	**Neuro**	**Neuro FI**	**Bowel**	**Urinary**	**Neuro**	**Neuro FI**	**Bowel**	**Urinary**	**Neuro**	**Neuro FI**
hEDS-TCS												
Total	78	78	78	78	76	76	76	76	60	60	60	60
Positive	26	76	77	63	5	15	42	7	1	12	28	17
Negative	52	2	1	15	71	61	34	69	59	48	32	43
% positive	33.3	97.4	98.7	80.8	6.6	19.7	55.3	9.2	1.7	20.0	46.7	28.3
TCS												
Total	38	38	38	38	35	35	35	35	29	29	29	29
Positive	13	25	38	32	3	7	25	7	1	8	21	3
Negative	25	13	0	6	32	28	10	28	28	21	8	26
% positive	34.2	65.8	100.0	84.2	8.6	20.0	71.4	20.0	3.4	27.6	72.4	10.3
P value (chi-squared)	0.92	0.00001	0.6	0.65	0.14	0.97	0.11	0.11	0.59	0.42	0.022	0.056

Intergroup comparison of clinical data of patients at the 3 visits. Cases with at least 1 moderate-severe symptom in the bowel, urinary, and neurologic ("Neuro") categories or a respective neurologic objective finding ("Neuro FI") were categorized as "positive" in a binary fashion at each visit. Chi-squared testing was applied to compare the 2 groups at each visit and in each symptom domain. The 2 groups differ significantly in the neurologic symptoms category at the third visit, indicating better subjective neurologic outcome in the hEDS-TCS relative to the typical TCS group ($P = 0.022$). The difference in the urinary symptoms at the first visit reflects that urinary symptom or pathologic urodynamics were mandatory inclusion criteria in the hEDS group, but not in the TCS group. Data are illustrated graphically in Figure 5.

Table 3. McNemar for Intragroup Testing of Outcome in Cases with Completed Follow-up

Group	TCS (n = 26)					hEDS-TCS (n = 59)				
Code	YY	NY	YN	NN	*P*	YY	NY	YN	NN	*P*
Bowel symptoms										
Visit 1-2	2	9	0	15	0.0076	3	0	19	37	<0.00001
Visit 1-3	1	0	10	15	0.004	1	0	18	40	<0.00001
Visit 2-3	1	0	1	24	1	2	0	3	54	0.25
Urinary symptoms										
Visit 1-2	6	0	10	10	0.0044	14	0	44	1	<0.00001
Visit 1-3	5	2	10	9	0.04	12	0	41	6	<0.00001
Visit 2-3	2	5	4	15	1	6	6	8	39	0.78
Neurologic symptoms										
Visit 1-2	19	0	7	0	0.02	32	1	26	0	<0.00001
Visit 1-3	19	0	6	1	0.04	27	1	30	1	<0.00001
Visit 2-3	17	2	2	5	1	19	0	23	17	<0.00001
Neurologic Findings										
Visit 1-3	3	0	19	4	<0.00001	8	4	23	24	0.0005

Clinical data of those 59 hEDS and 26 typical TCS patients with completed follow-up. The table shows the numbers of cases whose clinical condition was improved, unchanged, deteriorated and cases in whom no symptoms or findings were present. The McNemar test rejected the null hypothesis that surgery was not effective when comparing the results of the 1st versus 2nd and 1st versus 3rd visits. Comparing the 2nd versus 3rd visits, the test revealed a statistically significant improvement for the neurologic symptoms only and only in the hEDS group.
TCS, tethered cord syndrome; hEDS, hypermobile Ehlers-Danlos syndrome; Y, symptom/findings present; N, symptom/findings not present.

evidence that the human FT has indeed elastic properties. Further, we show in hEDS congenital and acquired collagen fibril abnormalities of the FT associated with biomechanical abnormalities.

Pathology and Biomechanics of the Filum Terminale

The applied tension test measures stretch forces in response to the elongation of the FT. It provides parameters (stress and strain) that are normalized for structures with different original length and different diameter. Therefore it is possible to compare the biomechanics of different specimens (e.g., muscle tendons with a filum terminale). Accordingly, observations in tendons that link abnormal biomechanics to morphologic findings of acquired collagen fibril damage[23,28] can be translated to better understand the FT pathology in TCS.

Our biomechanical findings show that the human FT of TCS patients has elastic properties like tendons and ligaments.[23,28] In analog to tendons that protect muscles and bones,[29] and as suggested by others,[25,27] the FT should be therefore able to elastically dampen spine movement–related stretch forces, eventually protecting the conus medullaris against neuronal stretch injury. Though both study groups had a diseased FT, the elastic properties were impaired in hEDS only. In hEDS the FT loses elasticity and becomes plastic at about 4% strain (relative elongation), significantly different from the TCS group without hEDS in which elasticity is maintained until 8% strain. For comparison, in fresh human cadavers without spine disease, history elasticity of the FT was maintained until 7% strain.[25] Beyond the elastic range and up to the maximum tested FT strain of 15%, in both groups the FT becomes plastic or, using another term, inelastic. However, we show that the plastic FT is associated with high FT stress in both study groups.

In tendons, collagen fibril microdamage occurs in response to elongations beyond the maximum elastic strain.[19-22,28] Such mechanical overload has been shown in tendons to trigger an immunologic cascade, which causes inflammation, further damaging the biomechanical properties.[19,28,30,31] Our morphologic studies show that the FT of hEDS cases was subjected to immunocyte invasion and collagen fibril microdamage, the latter statistically significant less frequent in typical TCS. Accordingly, morphologic observations indicate that in hEDS-TCS, but significantly less in typical TCS, the FT is operating beyond its maximum elastic strain. Therefore our morphologic observations mirror our biomechanical finding of a reduced maximum elastic strain of the FT in hEDS compared with typical TCS and cadaver specimens without known spine disease history.

In addition, we show with electron-microscopy that hEDS specifically affects the architecture of the collagen fibril bundles of the FT, leading to a loss of longitudinal fibril arrangement. According to TEM studies of skin specimens and skeletal tendons in CTD patients, those collagen abnormalities are specific to CTD and inherited and have also been linked to impaired biomechanical properties.[17,18] We suggest that inherited collagen abnormalities observed in the hEDS filum make it even more

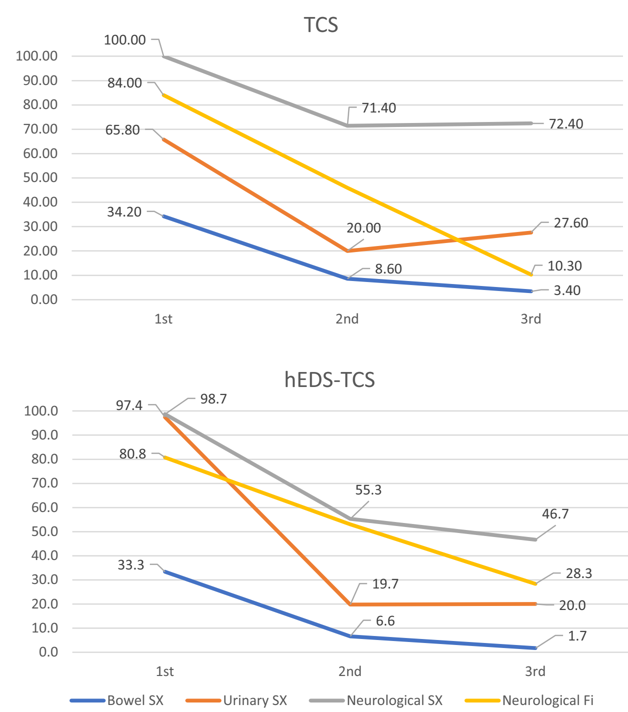

Figure 5. Percentage of patients presenting with at least 1 moderate or severe symptom or finding at each visit. Only cases with a completed 12-month postoperative follow-up are shown (59 hypermobile Ehlers-Danlos syndrome–tethered cord syndrome [TCS] and 26 TCS cases). Comparing the first (preoperative) with the second (3-month postoperative) visits and the first with the third visits (12-month postoperative), all differences are highly significant (McNemar test $P < 0.0001$). Comparing the second and third visits, only the improvement of neurologic symptoms reaches statistical significance. See Table 3 for detailed McNemar analysis results. FI, objective findings; SX, subjective symptoms.

susceptible to mechanical overload, which then starts the previously described sequela of acquired fibril damage, rendering the FT into a less elastic structure.

Wrapping up biomechanical and morphologic findings and considering the spine hypermobility seen in hEDS, we suggest that with hEDS comorbidity the FT and eventually the conus are exposed to supraphysiologic stretch forces, potentially causing stretch injury and TCS.

At the end, this pathology is quite similar to that in typical TCS, where spinal cord stretch injury has all along been attributed to traction forces caused by a radiologically diseased and/or shortened FT.[6,27]

The limited elastic elongation appears to be the major biomechanical finding in hEDS cases. It indicates that in hEDS the FT loses its elastic properties (i.e., the ability to temporarily stretch without structural damage to its fibrous structure, already at elongations almost 50% lower than the non-hEDS specimen). Clinically, such loss of elastic properties in hEDS appears as a permanent loss of stiffness of tendons,[18] joint hypermobility, skin extensibility, and tissue fragility in hEDS.[5]

Surgical Outcome of Filum Terminale Excision

We showed that our rigorous diagnostic approach excluding organic causes of tethered cord syndrome (i.e., strict formal clinical diagnosis of TCS, expert diagnosis of EDS, exclusion of spine disorders which could explain the observed symptoms) identified hEDS-TCS patients who generally benefit from FT excision. Outcome in the hEDS group was comparable or even superior to that of the TCS group with low-lying conus or fatty infiltration of the FT. Intragroup analysis revealed a statistically significant improvement in the neurologic-urinary-bowel categories in both study groups, supporting the indication for filum excision for both typical TCS and hEDS-TCS.

Table 4. Adverse Events

Hypermobile Ehlers-Danlos Syndrome	Diagnosis	Treatment
31-year-old female	Pseudomeningocele 4 months post surgery, cauda equina tethering 12 months post surgery	Excision and dural repair cauda equina release
34-year-old female	Fractured L3 spinous process likely a result of the interlaminar approach	Local revision
16-year-old female	Progressive kyphoscoliosis 18 months post	Extension of a previous T5 - L3 fusion to the sacral level
28-year-old female	New electric foot pain that affected mobility	Gabapentin medication
32-year-old female	Temporary urinary retention	catheterization
25-year-old female	Worsening of EDS-related pain	Wheelchair assistance pain medication
24-year-old female	Permanent worsening of coexisting dystonia	Neurologic management
27-year-old female	Worsening of preexisting shoulder twitching and dystonia	Temporary neurologic management
40-year-old female	Worsening of preexisting leg weakness	Temporarily increased assistance of wheelchair
50-year-old female	Worsening of preexisting leg weakness	Permanently increased assistance of wheelchair
Typical TCS		
30-year-old female	Worsening of diffuse body pain	Neurologic pain management
46-year-old female	Postoperative ileus	Medical treatment
9-year-old female	Worsening thoracic pain	Removal of preexisting thoracic arachnoid cyst
53-year-old female	Intraoperative filum hemorrhage with consecutive arachnoiditis	Removal of posthemorrhagic arachnoid cyst
27-year-old female	Cauda equina tethering	Cauda equina release

Limitations

In spinal cord disorders, it is generally difficult to assess the multiplicity of symptoms in a quantitative manner.[32] hEDS comorbidity adds a day-by-day fluctuating character, further challenging the assessment of symptoms in an intraindividually reproducible manner.[33] Ultimately, no validated quantitative scores or scales describing the symptomatology of TCS with or without hEDS comorbidity are currently available, and therefore we relied on clinician- and patient-reported assessments, which both are prone to investigator bias.

According to the STROBE guidelines, our study is classified as a prospective cohort study even without conservative treatment controls.[34,35] Such control groups were not included mainly for ethical reasons because our inclusion criteria required a deterioration of symptoms despite conservative treatment. Therefore our study does not reach the level of evidence of a randomized clinical trial (RCT) and our study can't prove that surgery in both typical and hEDS-TCS is superior to conservative treatment. Though understanding typical TCS is a gold standard for gauging the clinical data of EDS-TCS cases, our study shows that the outcome in the hEDS-TCS group is at least as good as in the TCS group. However, it should be noted that surgery for radiologically positive, typical TCS is generally accepted as an appropriate treatment procedure despite the fact that no RCT has shown its efficacy.[6,11] The only existing RCT looking at whether surgery is superior to conservative treatment in TCS investigated the FT transection in 10 pediatric cases with occult TCS and exclusively included patients with a urinary pathology, though not complete TCS. No benefit of surgery could be shown.[9] Eventually, all previous OTCS studies[8] failed to show a FT pathology and did not compare the outcome of surgery with "gold standard" typical TCS cases.

CONCLUSIONS

Our study revealed a pathology of the FT in TCS with hEDS comorbidity, potentially exposing the conus medullaris to stretch injury like in typical TCS. We propose that hEDS comorbidity should be considered as a biomarker for the identification of TCS patients who might benefit from FT excision even in the absence of radiographic evidence of a low-lying conus.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Petra M. Klinge: Conceptualization, Methodology, Investigation, Writing — original draft, Supervision. **Vikas Srivastava:** Investigation, Writing — original draft. **Abigail McElroy:** Investigation, Writing — original draft. **Owen P. Leary:** Project administration, Writing — original draft. **Zahra Ahmed:** Investigation, Writing — original draft. **John E. Donahue:** Investigation. **Thomas Brinker:** Conceptualization, Methodology, Writing — original draft. **Philippe De Vloo:** Writing — original draft. **Ziya L. Gokaslan:** Supervision, Writing — original draft.

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