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Original Article

Evaluation of cervical spine pathology in children with Loeys-Dietz syndrome

Marc Andrew Prablek[1], Melissa LoPresti[1], Brandon Bertot[2], Shaine Alaine Morris[3], David Bauer[4], Sandi Lam[5], Vijay Ravindra[6]

[1]Department of Neurosurgery, Baylor College of Medicine, Houston, Texas, [2]Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, Departments of [3]Cardiology and [4]Neurosurgery, Texas Children's Hospital, Houston, Texas, [5]Department of Neurosurgery, Lurie Children's Hospital, Chicago, Illinois, [6]Department of Neurosurgery, University of California San Diego, San Diego, California, United States.

E-mail: *Marc Andrew Prablek - prablek@bcm.edu; Melissa LoPresti - melissa.lopresti@bcm.edu; Brandon Bertot - brandon.bertot@bwh.harvard.edu; Shaine Alaine Morris - shainem@bcm.edu; David Bauer - dfbauer@texaschildrens.org; Sandi Lam - sandi.lam@northwestern.edu; Vijay Ravindra - vijay.ravindra@gmail.com

***Corresponding author:**
Marc Andrew Prablek,
Department of Neurosurgery,
Baylor College of Medicine,
Houston, Texas, United States.

prablek@bcm.edu

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ABSTRACT

Background: Loeys-Dietz syndrome (LDS) is a genetic connective tissue disorder associated with multiple musculoskeletal anomalies, including cervical spine instability. We sought to examine the nature of imaging for cervical spine instability in children with LDS due to likely pathogenic or pathogenic variants in *TGFBR1*, *TGFBR2*, *TGFB2*, *SMAD3*, or *TGFB3*.

Methods: A retrospective chart review was conducted, examining relevant data for all children with LDS screened at our institution from 2004 through 2021. Cervical spine X-rays were used to assess cervical instability, cervical lordosis, and basilar impression.

Results: A total of 39 patients were identified; 16 underwent cervical spine screening (56.25% male). Median age at initial screening was 7 years (Q1-Q3: 3.75–14, range: 0.1–19). Six of 16 patients evaluated (37.5%) had radiographical evidence of cervical instability. Mean angles of cervical lordosis were 20° (SD = 14.1°, range = 4°–33°) and 17.3° (SD = 16.4°, range = 2°–41°), respectively. Three patients demonstrated radiographical basilar impression. Radiographic progression of cervical instability was seen in one case. All but two were managed conservatively with observation, one patient underwent surgical fixation and fusion of C1-2, the other underwent complex cervical reconstruction anterior and posterior instrumentation.

Conclusion: Cervical spine evaluation is important in this cohort; we identified 37.5% had evidence of cervical spine instability, and many had concurrent spinal pathology. From our experience, we agree with the recent advisement for screening at diagnosis and for those previously diagnosed that have not undergone screening. Future study may outline more specific screening practices.

Keywords: Basilar impression, Cervical spine instability, Connective tissue disorder, Loeys-Dietz syndrome

INTRODUCTION

Loeys-Dietz syndrome (LDS) is a rare connective tissue disorder characterized by vascular, cardiac, skeletal, craniofacial, and cutaneous anomalies.[1,15,16] Due to abnormal connective tissue and ligamental laxity, this group may experience spinal pathology, including dural ectasia, scoliosis, cervical spine malformation, or cervical instability.[1,15,16] Given the fact that the pediatric cervical spine, at baseline, is hypermobile and less stable than the adult cervical spine,[18] LDS can

further impact stability, leading to subluxation or instability resulting in spinal cord impingement and potentially significant mortality and morbidity.

The frequency of cervical spine instability in LDS patients is poorly described in the literature, with a prevalence ranging from 16.3% to 100%.[5,7,16,23,25,26] Due to rarity of disease, understanding of disease pathology is continually evolving, reflected by the recent development of cervical spine screening recommendations for these patients. Therefore, we aimed to examine our experience with cervical spine evaluation in patients with LDS at a tertiary academic referral center. We sought to characterize cervical spine measurements, the incidence of basilar impression and cervical instability, and identify other cervical spinal anomalies in this cohort. We hypothesize that when screening is applied, it will help identify cervical instability and pathology that warrant further evaluation and monitoring in these complex patients.

MATERIALS AND METHODS

With the Institutional Review Board approval, a retrospective review was performed to identify all patients diagnosed with LDS at Texas Children's Hospital – Baylor College of Medicine, a tertiary academic referral center, cared for between 2005 and 2018. Patients diagnosed <19 years of age were identified from the institutional Cardiovascular Genetics Program database. LDS diagnosis was defined as presence of a pathogenic or likely pathogenic variant in *TGFBR1*, *TGFBR2*, *TGFB2*, *SMAD3*, or *TGFB3* in conjunction with phenotypic features of LDS, including aortic dilation, arterial tortuosity, and/or craniofacial features. Screening for cervical instability in this study was defined as undergoing cervical spine X-rays. Those without appropriate C-spine imaging were excluded from the study.

Demographic and clinical information examined included age, sex, race/ethnicity, affected gene, symptoms, reason for screening, functional status defined by modified Rankin scale, and management strategy for cervical spine instability if applicable. Due to the retrospective nature of the study, screening was unstandardized and at the discretion of the provider. Screening indications included asymptomatic patients to achieve a baseline or before a procedure which may require intubation or in an area near the cervical spine, symptoms such as neck pain, other spinal pathology to fully evaluate the spine, or neurological complaints localized to the cervical spine. Radiographical data collected included time and interval between X-rays when available, presence of cervical spine instability on X-ray, presence of scoliosis, presence of additional spinal pathology, basilar impression, and cervical lordosis. Descriptive statistics were calculated.

Radiologic parameters measured

Cervical lordosis and basilar impression were assessed on neutral cervical spine X-rays using commonly accepted cervical spine measurements including the Jackson physiological stress lines angle, the C2–C7 Cobb angle, the C2–C6 Cobb angle, as well as the McGregor, Chamberlain, and McRae lines, shown using representative lateral films in [Figure 1].

The Jackson physiological stress lines and C2–C7 Cobb angle were used to assess the degree of cervical lordosis.[10] The Jackson physiological stress lines were assessed using two lines, one parallel to the posterior surface of the C2 vertebral body and the other parallel to the posterior surface of the C7 vertebral body; the angle at their intersection assessed cervical lordosis [Figure 1a].[12,22] The C2–C7 Cobb angle was measured by the angle of the perpendicular lines of the parallels of the inferior endplate of the C2 and C7 vertebrae [Figure 1b].[11,22] In cases where the C7 vertebral body could not be visualized on cervical spine X-ray, the C2–C6 Cobb angle, an acceptable alternative, was used to assess cervical lordosis [Figure 1c].[27]

The McGregor, Chamberlain, and McRae lines were used to identify basilar impression.[13] The McGregor line was drawn from the posterior end of the hard palate to the most inferior portion of the occipital curve, [Figure 1d][13,20] defined as positive if the apex of the dens was >4.5 mm above this line.[13,20] The Chamberlain line was drawn from the posterior end of the hard palate to the opisthion, [Figure 1e][3,13] defined as positive if the apex of the dens extended >3 mm above this line.[3,13] Finally, the McRae line was drawn from the basion to the opisthion, [Figure 1f][13,21] defined as positive if the tip of the dens extended past this line.[13,21]

Based on standard clinical criteria, cervical instability was defined in dynamic lateral radiographs as spondylolisthesis or retrolisthesis of one vertebral body on another that changed >2 mm between flexion and extension films.

RESULTS

Of the 39 children treated for LDS at our institution during the study period, 16 (41.02%) were evaluated for cervical instability with cervical spine flexion and extension X-rays [Table 1]. Cervical spine evaluations occurred from 2005 to 2019, increasing after guidelines for screening were recommended in 2015. Nine (56.25%) were male; 7 (43.75%) were female. Nine (56.25%) were Hispanic White, 4 (25%) non-Hispanic White, 2 (12.5%) Asian, and 1 (6.25%) African-American. Genes affected included *TGFBR2* in 6 patients (37.5%), *TGFBR1* in 4 (25%), *TGFB2* in 5 (31.25%), and *SMAD3* (homozygote) in 1 (6.25%). The median age at initial screening was 7 years (Q1–Q3: 3.75–14, range: 0.1–19).

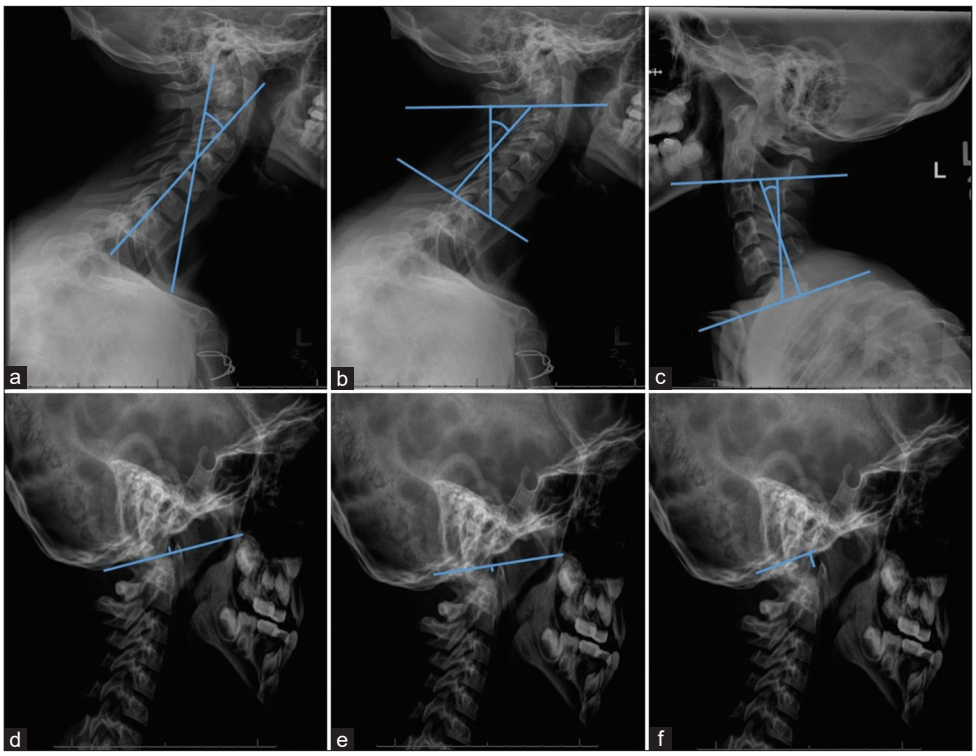

Figure 1: Representative lateral C-spine X-rays chosen to demonstrate: (a) Jackson physiological stress lines angle, (b) C2–C7 Cobb angle, (c) C2–C6 Cobb angle, (d) McGregor line, (e) Chamberlain line, and (f) McRae line.

Cervical spine screening

Sixteen patients underwent initial evaluation; three patients underwent additional imaging after their initial screen. In these patients, the mean interval between imaging was 275 days (SD 223, range 55–491, [Table 2]). Thirteen patients (81.25%) were asymptomatic at time of screening and underwent screening to rule out cervical pathology. Two patients (cases 1 and 7) underwent c-spine screening secondary to complaints of neck pain. In case 1, screening was normal, but in case 7, cervical instability requiring surgery was identified. Finally, another patient (case 10) was screened for cervical instability preoperatively in anticipation of ventricular septal defect repair to rule out subluxation before intubation. No subluxation was seen, but focal kyphosis and hypoplasia at the C3 vertebrae were identified [Figure 2]. The patient underwent cardiothoracic surgery, and follow-up imaging 113 days after initial imaging confirmed kyphosis, hypoplasia at C3, and anterior subluxation of C2 on C3 by 3.3 mm; most recent films at 442 days showed progression to 4.5 mm anterolisthesis of C2 on C3. However, the patient remained clinically stable with no neurological deficits, managed with observation. One other patient (case 4) who received follow-up imaging after initial screening in the setting of an abnormal MRI for scoliosis evaluation had 2 mm of anterolisthesis of C2 on C3, though subsequent flexion and extension X-rays were normal. One patient (case 16) underwent initial screening for neck pain and was found to have significant atlantoaxial instability prompting C1–2 fixation and fusion.

Cervical spine instability

Evaluation of cervical spine flexion-extension radiographs revealed cervical instability in 6 (37.5%) patients with LDS screened [Table 3]. Of these, three had atlantoaxial instability (cases 12, 13, and 16), and three had subaxial instability (cases 6, 7, and 10). Four were treated with observation, while one patient (Patient 15) underwent surgical C1–2 fixation and fusion, and another patient (case 7) underwent C5–6 corpectomy with anterior column reconstruction and fixation of occiput to T2. Surgery was recommended for one additional patient (case 6); however, parents elected for continued observation after consultation for a second opinion.

Cervical spine curvature

[Table 2] demonstrates the radiographic parameters assessed for each case, including follow-up, if present. Assessment of cervical lordosis using the Jackson physiological stress lines and C2–C7 Cobb angle required lateral view cervical spine radiographs, available in seven patients (cases 1, 3, 4, 6, 10, 11, and 16). From these seven, the average angle of cervical

Table 1: Demographic, clinical, and screening data.

	***n*=16**
Mean (SD, range) age at screening (years)	8.8 (SD 5.9, range 0.1–19)
Sex, *n* (%)	
Male	9 (56.25%)
Female	7 (43.75%)
Race/ethnicity, *n* (%)	
Non-Hispanic White	4 (25%)
Hispanic White	9 (56.25%)
Asian	2 (12.5%)
African-American	1 (6.25%)
Affected gene, *n* (%)	
TGFBR1	3 (18.75%)
TGFBR2	7 (43.75%)
TGFB2	5 (31.25%)
TGFB3	0 (0%)
SMAD3	1 (6.25%)
Reason for initial screening, *n* (%)	
Asymptomatic screening	13 (81.25%)
Neck pain	2 (12.5%)
Preoperative assessment	1 (6.25%)
Presence of cervical instability, *n* (%)	6 (37.5%)
Presence of scoliosis, *n* (%)	8 (50%)
Presence of other spinal pathology*, *n* (%)	4 (25%)
Number of total screenings, *n* (%)	
1	14 (87.5%)
2	1 (6.25%)
3	1 (6.25%)
Average time between screenings (days)	275 (SD 223, range 55–491)
Functional outcomes (mRS) at last follow-up, *n* (%)	
0–2	15 (93.75%)
3–6	1 (6.25%)

mRS: modified Rankin scale, SD: Standard deviation. *Additional spinal pathology was L5-S1 spondylolisthesis in cases 4, 11, and 12.

lordosis associated with the Jackson physiological stress lines in the lateral view was 20° (SD 14.1°, range 4°–33°). The average C2–C7 Cobb angle in the lateral view was 17.3° (SD 16.4°, range 2°–41°). For case 11, the C2–C7 Cobb angle could not be assessed, thus the C2–C6 Cobb angle was measured instead, revealing cervical lordosis of 20° [Table 2]; thus, this measurement was excluded when calculating the average C2–C7 Cobb angle.

Basilar impression

Regarding assessment of basilar impression using the McGregor, Chamberlain, and McRae lines, two patients (cases 6 and 11) showed radiologic evidence of basilar impression [Table 2]. Case 11 had positive McGregor and Chamberlain lines, but a negative McRae line. Case 6 had positive McGregor, Chamberlain, and McRae lines. The average distance by which the tip of the dens extended beyond the McGregor line in cases 6 and 11 was 5.9 mm (SD 0.35 mm, range 5.6–6.1 mm). The average distance by which the tip of the dens extended beyond the Chamberlain line in cases 6 and 11 was 5.1 mm (SD 1.20 mm, range 4.2–5.9 mm). In the one case, where the tip of the dens extended beyond the McRae line (case 6), it did so by 0.5 mm.

Evidence of radiographic progression

Three cases (4, 10, and 16) had at least two sets of cervical spine radiographs to allow for comparison and evaluation of progression. The mean time between screening was 311 days (SD 189.6, range 113–491). However, cases 10 and 16 had incomplete follow-up imaging, lacking lateral view cervical spine radiographs. Thus, progression was assessed in case 4; the C2–C7 Cobb angle decreased by 22°, while the tip of the dens fell below McGregor, Chamberlain, and McRae lines by 0.3 mm (previously 1.6 mm), 1.6 mm (previously 1.9 mm), and 4.6 mm (previously 2.5 mm), respectively [Table 2]. Changes in the Jackson physiological stress lines angle could not be assessed in case 4 due to poor vertebral body visualization on follow-up imaging [Table 2].

Other identified spinal pathologies

Of the 16 patients screened for cervical instability, 8 (50%) had concurrent scoliosis and 4 (25%) had other concurrent spinal pathology, identified as L5-S1 spondylolisthesis [Table 1]. Of the six patients with radiographic evidence of cervical instability, four had scoliosis (66.7%) and three had L5-S1 spondylolisthesis (50%). One patient (case 9) had a combination of C3 subaxial hypoplasia, focal cervical kyphosis, and cervical subaxial instability [Figure 2]. No other spinal pathologies were identified in this group.

DISCUSSION

We report our institutional experience with evaluation for cervical spine instability in pediatric patients with LDS. We found an increase in evaluation after guidelines promoted screening. We also found that younger patients tended to be screened more than older patients. From the radiographs of those evaluated, we identified cervical instability, mildly reduced cervical lordosis, and basilar impression among other spinal pathologies in this group. Based on our findings, we underscore the importance of screening, highlight the pathology to recognize and follow, and promote development of a multidisciplinary team to help improve care and inform screening in this population.

Etiology of cervical spinal pathology in LDS

The predisposition to develop cervical pathology, as with other manifestations of LDS, occurs as a result of the

Table 2: Radiologic parameters assessed in patients screened for cervical spine instability with follow-up.

Case	Gene and variant (transcript)	Imaging interval (days)	View	Jackson physiological stress lines angle	C2–C7 Cobb angle	McGregor line (mm)	Chamberlain line (mm)	McRae line (mm)
1	*TGFBR2*	0	Lateral	4°	2°	+0.7	−3.2	−8.1
	c.1563G>A		Flexion	32°	49°	+2.5	+0.6	−3.5
	p.Trp521Ter		Extension	66°	56°	−0.6	−4.6	−11.8
	(NM_003242)							
2	*TGFBR2*	0	Lateral	UTA	UTA	UTA	UTA	UTA
	c.1238T>A		Flexion	26°	40°	UTA	UTA	UTA
	p.Leu438Gln		Extension	57°	54°	−2.6	−6.1	−20.3
	(NM_003242)							
3	*TGFBR2*	0	Lateral	32°	41°	+4.4	+1.5	−9.1
	c.1336G>A		Flexion	31°	26°	+12.1	+6.7	−3.1
	p.Asp471Asn		Extension	48°	60°	+6.5	+2.3	−9.2
	(unknown)							
4	*TGFBR2*	0	Lateral	6°	26°	−1.6	−1.9	−2.5
	DNA variant not		Flexion	46°	49°	+0.4	−3.6	−6.4
	available		Extension	60°	62°	+3.4	+1.9	−7.9
	p.Arg528His	491	Lateral	UTA	4°	−0.3	−1.6	−4.6
	(unknown)		Flexion	59°	53°	−2.4	−4.2	−6.2
			Extension	56°	65°	+3.2	+1.1	−7.1
		Average†	Lateral	6°	15°	−1.0	−1.8	−3.6
			Flexion	52.5°	51°	−1.0	−3.9	−6.3
			Extension	58°	63.5°	+3.3	+1.5	−7.5
5	*TGFBR2*	0	Lateral	UTA	UTA	UTA	UTA	UTA
	c.1583G>A		Flexion	27°	39°	−0.6	−2.2	−6.5
	p.Arg528His		Extension	54°	40°	−9.2	−10.1	−15.7
	(NM_003242)							
6	*TGFBR2*	0	Lateral	UTA	2°	+6.1	+5.9	+0.5
	c.859T>C		Flexion	67°	65°	+9.1	+7.3	−1.5
	p.Trp287Arg		Extension	58°	46°	+16.5	+15.5	+7.7
	(NM_003242.5)							
7	*TGFBR1*	0	Lateral	UTA	UTA	UTA	UTA	UTA
	c.797A>G		Flexion	12°	20°	+14.9	+8.6	−10.5
	p.Asp266Gly		Extension	38°	34°	+8.8	+5	−8.2
	(NM_004612)							
8	*TGFBR1*	0	Lateral	UTA	UTA	UTA	UTA	UTA
	9q22.3q31.3 del.		Flexion	2°	2°	+5.9	+5.2	−13.3
	(complete del. of		Extension	34°	24°	−3.2	−4.1	−8.1
	TGFBR1)							
9	*TGFBR1*	0	Lateral	UTA	UTA	UTA	UTA	UTA
	c.1198G>A		Flexion	21°	7°	+6.8	+5.3	−5.1
	p.Asp400Asn		Extension	49°	50°	−0.8	−1.5	−7.8
	(NM_004612.2)							
10	*TGFBR1*	0	Lateral	25°	4°	−2.6	−4.3	−1.4
	c.829T>A		Flexion	25°	15°	−0.1	−0.9	−1.0
	p.Trp277Arg		Extension	UTA	53°*	−6.8	−9.2	−10.2
	(NM_004612.2)	113	Lateral	UTA	UTA	UTA	UTA	UTA
			Flexion	UTA	55°*	−3.4	−4.7	−5.3
			Extension	UTA	0°	−6.2	−7.5	−9.0
		442	Lateral	UTA	UTA	UTA	UTA	UTA
			Flexion	43°	54°	+1.0	−1.8	−1.9
			Extension	31°	36°	−7.8	−10.8	−12.6
		Average†	Lateral	25°	4°	−2.6	−4.3	−1.4
			Flexion	34°	34.5°	−0.8	−2.5	−2.7
			Extension	31°	18°	−6.9	−9.2	−10.6

(Contd...)

Table 2: (*Continued*).

Case	Gene and variant (transcript)	Imaging interval (days)	View	Jackson physiological stress lines angle	C2–C7 Cobb angle	McGregor line (mm)	Chamberlain line (mm)	McRae line (mm)
11	*SMAD3*	0	Lateral	UTA	20°*	+5.6	+4.2	−7.3
	homozygous		Flexion	UTA	UTA	+5.4	+0.5	−8.0
	c.532+2T>A		Extension	UTA	UTA	−2.1	−2.4	−13.9
	(NM_005902.3)							
12	*TGFB2*	0	Lateral	UTA	UTA	UTA	UTA	UTA
	c.458G>A		Flexion	28°	39°	−10.0	−11.6	−22.5
	p.Arg153His		Extension	37°	30°	−13.9	−16.9	−19.3
	(NM_003238)							
13	*TGFB2*	0	Lateral	UTA	UTA	UTA	UTA	UTA
	1q41 deletion		Flexion	16°	39°	−1.9	−3.6	−8.4
	(complete del. of *TGFB2*)		Extension	76°	66°	+1.8	−2.3	−12.9
14	*TGFB2*	0	Lateral	UTA	UTA	UTA	UTA	UTA
	c.904C>T		Flexion	17°	28°	+1.3	−7.3	−8.1
	p.Arg302Cys		Extension	73°	69°	+6.3	+4.3	−1.6
	(NM_003238)							
15	*TGFB2*	0	Lateral	UTA	UTA	UTA	UTA	UTA
	c.904C>T		Flexion	56°	58°	−2.2	−4.1	−15.0
	p.Arg302Cys		Extension	67°	62°	−0.1	−3.9	−13.6
	(NM_003238)							
16	*TGFB2*	0	Lateral	UTA	UTA	UTA	UTA	UTA
(16)	c.905G>A		Flexion	24°	30°	−3	−5.7	0
	p.Arg302His		Extension	65°	63°	−6	−7.1	−4.6
	(NM_003238)	55	Lateral	33°	37°	+4	+1	−2
			Flexion	0°	8°	0	−2	−4.5
			Extension	43°	59°	0	0	−1
		Average†	Lateral	33°	37°	+4	+1	−2
			Flexion	12°	19°	−1.5	−3.85	−2.25
			Extension	54°	61°	−3	−3.55	−2.8

UTA: Unable to assess, del.: Deletion. Imaging interval day 0 denotes the 1st day each patient was screening, with follow-up interval numbered by the length of follow-up in days from initial screen. †For the purposes of calculating averages and standard deviations for the overall cohort, in patients with multiple flexion and extension films of the cervical spine (cases 4 and 12), the average Jackson physiological stress lines angle, C2–C7 Cobb angle, McGregor, Chamberlain, and McRae line distances were calculated for each view. *C2–C6 Cobb angle was used instead, due to inability to visualize the C7 vertebrae. Positive sign indicates the distance of the tip of the dens above either the McGregor, Chamberlain, or McRae lines. Negative sign indicates the distance of the tip of the dens below either the McGregor, Chamberlain, or McRae lines. All variants were heterozygous except case 9.

altered TGF-β signaling pathway.[1,4] The TGF-β signaling pathway is normally involved in a multitude of physiologic processes including the deposition of extracellular matrix and development of bone, cartilage, and blood vessels.[1,4] Hence, when this pathway is altered, as in LDS, ligamentous laxity and abnormal connective tissue development ensue, enabling the conditions in which cervical instability can occur.[7] While much of the LDS literature reports the implication of alterations in this signaling pathway related to arterial dilation and dissection, it is our belief that similar changes to the connective tissue involved in cervical spine stability, including ligaments, facet joint capsules, and intervertebral disc spaces, are impacted by changes in this pathway. We postulate that it is because of this, in addition to the mobile cervical spine in children, disproportionate size of head to body, and weaker neck muscles in children,[2,6] that underscores the importance of screening, diagnosis, and treatment when indicated to preserve cervical spine stability and function in these growing patients.

Role of cervical spine evaluation in pediatric patients with LDS

Cervical spine instability in patients with LDS is reported widely in the literature,[5,7,16,23,25,26] therefore, evaluation is an important surveillance tool to identify potentially serious pathology and monitor for progression. We identified a 37.5% prevalence of cervical instability among those evaluated in our series. Furthermore, of those with cervical instability, there was a 1:1 ratio of atlantoaxial to subaxial instability,

Table 3: Cases with cervical instability findings and treatment.

Case	Radiologic findings	Treatment
6	Abnormal facet alignment of C5–6 and C6–7 with facets that appear nearly perched upon each other particularly with flexion and then with extension there appears to be near perched appearance of C6–7 posterior facets.	Surgery, C5–7 anterior cervical discectomy and fusion, recommended, though family elected for observation
7	Severe cervical kyphosis centered at C5–6, with hypermobility and global hyperlordosis.	Surgery, C5–6 anterior cervical corpectomy and anterior column reconstruction, occiput-T2 fixation/fusion
10	Focal kyphosis at the hypoplastic C3 vertebra measuring 39 degrees when neutral, 42 degrees with flexion, and resolution with extension. On follow-up, anterior subluxation of C2 on C3 shows minimal change with flexion-extension. On further follow-up, the 4.5 mm anterolisthesis of C2 on C3 reduced completely on extension.	Observation
12	Anterior translation of C1 relative to C2, with the anterior atlantodens interval measuring 5mm with flexion and 1.5 mm with extension.	Observation
13	The atlantodens interval measures 7 mm on flexion.	Observation
16	Abnormally large atlantodental interval which changes drastically on change of position from flexion to extension.	Surgery, C1–2 posterior instrumented fusion with iliac crest graft

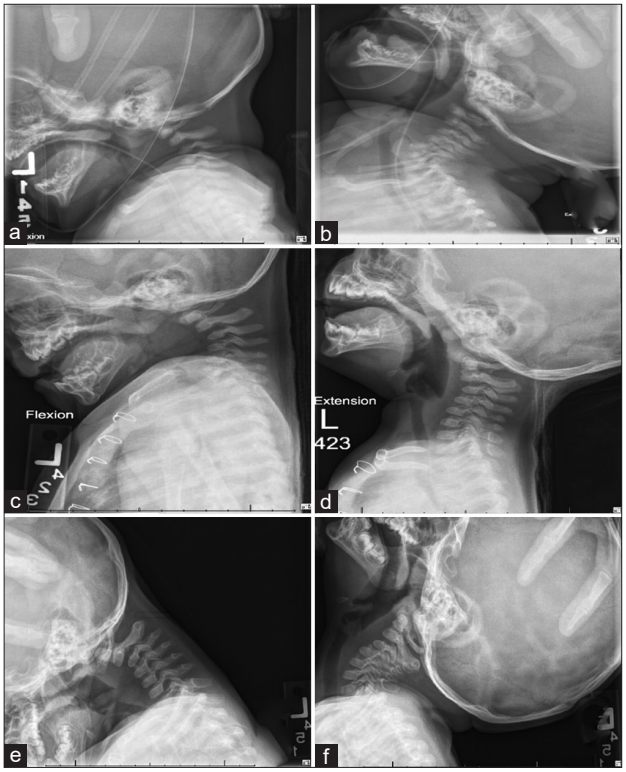

Figure 2: Preoperative cervical spine (a) flexion and (b) extension films at initial screening show slightly hypoplastic C3 vertebra, focal kyphosis at C3 measuring 42° with flexion that reduces to 11° with extension, and cervicothoracic junction lordosis measuring 27° with flexion and 64° with extension. Follow-up cervical spine (c) flexion and (d) extension films at 113 days follow-up demonstrate mild hypoplasia of C3, focal kyphosis with apex at C3 that increases with flexion, and anterior subluxation of C2 on C3 with minimal change in flexion and extension. Follow-up cervical spine (e) flexion and (f) extension films at 442 days follow-up demonstrate 4.5 mm of anterior motion of C2 on C3 in flexion that reduces in extension.

aligning with the results seen in Fuhrhop *et al*. (8:9 ratio of atlantoaxial to subaxial instability).[7]

Reviews of literature and expert opinion on LDS recommend cervical spine flexion and extension X-rays at the time of initial diagnosis.[7,15,19] If the child has normal initial cervical spine films, then they should be repeated every 3–5 years throughout growth and after any surgeries on adjacent areas of the spine.[19] In addition, evaluation should be performed if new neurologic symptoms develop and before any surgeries requiring intubation or procedures involving neck manipulation.[7,15] In our study, we found a suboptimal percent of children with LDS evaluated for cervical instability (16/39 patients) but an increase in screening after screening recommendations was instituted. In addition, for patients being managed chronically with a remote diagnosis, new screening recommendations were less often employed. Given the retrospective nature of this study, it is difficult to speculate why this is the case. It is possible that MRI/MR angiography of the spine is more frequently ordered to evaluate connective tissue and vascular pathology.[17] Nevertheless, plain radiographs, and especially flexion/extension radiographs, are an important modality for assessing cervical ligamentous instability. The optimal screening protocol likely involves a combination of multiple imaging modalities to identify different pathologies. Our findings reinforce the importance of recommended screening guidelines, as well as promoting increased awareness of cervical ligamentous instability in patients with LDS. To encourage a standardized approach to universal screening, we support a coordinated care team, multidisciplinary approach, and early consultation with a spine surgeon should cervical abnormalities be identified.[17] Furthermore, in light of various spinal and neurovascular diseases associated with an LDS diagnosis, we postulate that initial consultation with a neurosurgeon, with expertise in treating LDS, at

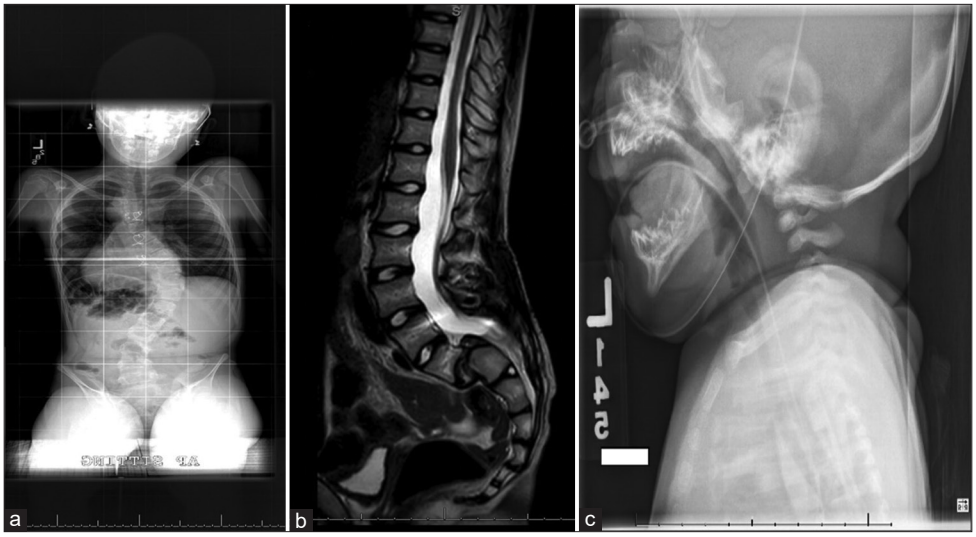

Figure 3: In addition to cervical instability, other spinal pathology is identified in LDS patients including (a) scoliosis, (b) spondylolisthesis, and (c) vertebral hypoplasia.

time of diagnosis may be helpful in following screening and surveillance imaging, interpreting relevant findings, guiding management, and discussing lifetime risk with patients and families. Alternatively, consultation with an orthopedic spine surgeon can also help guide management of cervical spinal pathologies and thoracolumbar scoliosis in this group.

The first step of treatment is identification of the pathology, underscoring the importance of screening. However, treatment of subclinical or preclinical disease requires caution and weighing of risks and benefits when determining the most appropriate treatment for these complex patients with multiple medical comorbidities and often asymptomatic cervical disease. The literature reports a range of treatments, including observation, bracing, traction, and corrective surgery.[5,7,15,24] Our study describes a cohort treated largely with observation for asymptomatic findings. For symptomatic patients, overall, corrective surgery is favored over bracing or traction due to a more definitive fixation and concern regarding the lasting impact of bracing or traction due to ligamental laxity.[5] However, bracing until definitive fusion can be performed is a viable option to prevent further progression of deformities and neurologic deterioration.[7] Most importantly, patients should be managed on a case-by-case basis, accounting for clinical status, comorbidities, and signs and symptoms of pathology in addition to radiographic findings.

Other considerations

We also highlight other key features of cervical changes in children with LDS. We found that the mean Jackson physiological stress lines angle was 20°, the mean C2-C7 Cobb angle was 17.3°, and the one C2–C6 Cobb angle was 20°. Among the general population, the normal configuration of the cervical spine is lordotic,[10] with mean cervical lordosis angles of either 21–22°[8] or 34°.[9] Therefore, while cervical lordosis is maintained, the degree may be mildly reduced in this population. It is unknown if this may contribute to spondylolisthesis, deformity, or instability overtime; therefore, we interpret this finding to further encourage surveillance for monitoring purposes. In addition, basilar impression can occur in this group.[7,14] We found the average distance by which the dens extended beyond McGregor's line to be 5.9 mm; in Fuhrhop *et al*., the mean distance was 8.5 mm for asymptomatic patients and 10.6 mm for symptomatic patients.[7] This difference may be due to our smaller sample size, our use of cervical spine radiographs rather than computed tomography for measurements, or asymptomatic cohort indicating preclinical or subclinical disease. However, the identification of basilar impression in children with LDS highlights the need for follow-up to avoid myelopathy and neurological sequela.

Cervical spine imaging in LDS patients may reveal additional abnormalities. C1 abnormalities, such as anterior and/or posterior arch defects as well as C1 hypoplasia, and C2 pathologies, including dens elongation, apex anterior angulation of the dens, off center location of the dens, and spondylolysis, can be present.[5,7] Patients can also have subaxial vertebral hypoplasia, focal kyphosis, and C1–C2 or C2–C3 subluxation.[5,7] In addition, patients may have other thoracolumbar pathology including scoliosis and spondylolisthesis. [Figure 3] represents various spinal pathologies associated with LDS diagnosed in our cohort. Given the breadth of disease and implications, comprehensive screening and management in this group is paramount.

Limitations

There are several limitations in our study. Due to the rarity of LDS, the small cohort of patients in our study limits our ability to draw statistically significant conclusions from our data or makes gene-based associations with findings. In addition, the suboptimal screening rate among our cohort, as well as the limited number of those with repeat screenings, perhaps due to developing understanding of disease pathology and evolving recommendations over time, precludes our ability to draw statistically significant conclusions. The retrospective study design also precludes our ability to prospectively assess screening recommendations or subsequently applied changes in management to truly evaluate efficacy of screening protocols. Finally, variability in types of and completeness of radiographs obtained, further limited our ability to assess both cervical spine curvature and basilar impression in all patients, thus reducing our power.

CONCLUSION

Patients with LDS are at risk for a myriad of spinal pathology, including cervical instability and basilar impression. We explored our experience with cervical spine instability evaluation in a pediatric cohort with LDS to identify the pathology diagnosed with screening to help inform and improve the role of screening in management in this group. We found that while screening was not universal, there was a 37.5% prevalence of cervical spine instability, presence of reduced cervical spine lordosis, and basilar impression in conjunction with other spinal abnormalities. We believe our results underscore the benefits of screening in these children, congruent with recommendations in the literature. Future studies may target more specific screening guideline improvements, including set intervals, and inform future treatment protocols.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

S.A.M. serves on the Scientific Advisory Board for Aytu biopharma for development of a clinical trial for vascular Ehlers-Danlos syndrome.

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