High Prevalence of Cervical Deformity and Instability Requires Surveillance in Loeys-Dietz Syndrome

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Background: Loeys-Dietz syndrome is a connective tissue disorder characterized by vascular, craniofacial, and musculoskeletal malformation. Our goal was to report the manifestations, surgical treatment, and complications in the cervical spine in patients with Loeys-Dietz syndrome.

Methods: We reviewed the clinical and cervical spine imaging data of eighty patients with Loeys-Dietz syndrome who were seen at our institution from January 2005 through January 2014. Their mean age at presentation was 17.3 years (range, three months to seventy-five years). We tested associations with use of the Fisher exact test (type of TGF- β R [transforming growth factor-beta receptor] mutation and cervical abnormalities) and the Student t test (age at presentation and type of TGF- β R mutation) (significance, $p = 0.05$).

Results: Vertebral anomalies and cervical instability were common; we found no significant association of TGF- β R-type with cervical abnormalities or age at presentation. Twenty-eight patients had atlas defects (anterior and/or posterior arch defects or hypoplasia), fifty-three had axis malformations (elongation, apex-anterior dens angulation, or spondylolysis), and twelve had focal kyphosis. Ten patients had hypoplastic subaxial vertebrae, leading to focal kyphosis (eight) and subaxial instability (nine). Eight patients had atlantoaxial instability. Of the thirteen patients with cervical instability, nine were treated surgically: fusion (eight patients) and halo application (one) (mean age, four years; range, three months to twelve years). Postoperative complications (seven patients) were pseudarthrosis, failure of fixation, junctional kyphosis or instability, and development of occipital-cervical instability.

Conclusions: Cervical midline defects (most often C1-C3) are common in Loeys-Dietz syndrome. Patients have a high prevalence of cervical instability, particularly a pattern of instability at C2-C3 associated with C3 vertebral body hypoplasia and C2-C3 focal kyphosis. Patients requiring surgery typically present in early childhood.

Level of Evidence: Therapeutic Level IV. See Instructions for Authors for a complete description of levels of evidence.

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Loeys-Dietz syndrome is an autosomal-dominant connective tissue disorder caused by mutations in the transforming growth factor-beta receptor 1 (TGF- β R1) or 2 (TGF- β R2) genes. The syndrome, first described in 2005¹, is characterized by a triad of aggressive aneurysm formation, hypertelorism, and bifid uvula or cleft palate¹. Common features include cutaneous manifestations (e.g., translucent skin and easy bruising), craniofacial abnormalities (e.g., craniosynostosis, retrognathia, and malar hypoplasia), and musculoskeletal findings

(e.g., joint hypermobility, arachnodactyly, talipes equinovarus, pectus excavatum or carinatum deformity, scoliosis, spondylolisthesis, and cervical spine malformations)¹⁻⁴.

Recognition of the features of Loeys-Dietz syndrome may facilitate early diagnosis, which is critical for treatment. The vascular abnormality is more pronounced than in other connective tissue disorders⁵, requiring early initiation of antihypertensive medication and frequent imaging surveillance to manage aneurysms². Although cervical spine abnormalities

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Fig. 1-A

Fig. 1-B

Sagittal computed tomogram (**Fig. 1-A**) and T2-weighted sagittal magnetic resonance image (**Fig. 1-B**) of an eight-year-old girl with C2 apex-anterior dens angulation (33°, measured in red), basilar impression, and hypoplastic C1 located within the posterior arch of C2. These osseous deformities resulted in cervicomedullary junction compression and motor weakness, requiring suboccipital craniectomy and C1 laminectomy at eleven years of age.

are common, information about patient age and the clinical presentation of cervical spine abnormalities, management, and treatment challenges is limited.

Our goal was to report the manifestations, surgical treatment, and complications in the cervical spine of patients with Loeys-Dietz syndrome.

Materials and Methods

Patient Population

After obtaining approval and a consent waiver from our institutional review board, we retrospectively reviewed the records of 122 patients with Loeys-Dietz syndrome (confirmed by genetic testing of the TGF- β R1 and TGF- β R2 genes) seen at our institution, a large referral center for such patients, from January 2005 through January 2014. Patients were referred primarily for genetic testing; some had already established orthopaedic treatment at other institutions. Although clinical and imaging records from these sites were requested, some cervical spine records were incomplete. Of the 122 patients, eighty (study cohort) had cervical spine images, radiology reports, and clinical records.

The mean age of the patients (forty female and forty male) was 17.3 $\pm$ 16.2 years (range, three months to seventy-five years); fifty-five (69%) were less than eighteen years of age. Twenty-two (27.5%) of the patients had mutations of the TGF- β R1 gene and fifty-eight (72.5%), the TGF- β R2 gene. The mean age at surgery was four years (range, three months to twelve years).

Clinical data included presence of symptoms related to the cervical spine, and timing, modality, and complications of previous cervical spine treatment. We examined all patients; all but one had undergone surgery for cervical deformity before examination.

Imaging data were obtained from head and neck CT (computed tomography) for seventy-one patients and from lateral radiographs for eighty

patients. Sixty-eight patients had lateral flexion and extension radiographs; the remaining patients had only neutral radiographs. From the images, we examined several vertebral abnormalities (vertebral hypoplasia or fusion defects; spondylolysis; and dens elongation, apex-anterior angulation, basilar impression, or off-center location), focal cervical kyphosis, and cervical instability.

Measurements and Definitions

Dens height was measured from the dens apex to the anterior-inferior aspect of the C2 vertebral body. Elongation was defined as a height two standard deviations (SDs) above the mean of historic controls⁶ (2.34 ± 0.22 cm), reduced by 15% for magnification correction⁷. To our knowledge, apex-anterior dens angulation has no standard definition; we defined it as an angle of $>25^\circ$ between the posterior cortex of the C2 body and that of the odontoid process (Figs. 1-A and 1-B). Basilar impression and invagination were defined using the McGregor line⁸. Basilar impression was considered present if the tip of the odontoid projected ≥ 5 mm above the McGregor line. Off-center dens location was determined by measuring the bilateral distances from the center of the dens to the medial aspect of the lateral masses of C1. If the ratio of these two measurements was <0.67 (a symmetric ratio being 1.0), the dens was considered off-center (Fig. 2).

Focal kyphosis was a term used if three or fewer vertebral bodies produced a kyphotic Cobb angle of $>15^\circ$.

Atlantoaxial instability was defined as an atlantodens interval of >5 mm in flexion. When flexion and extension radiographs were unavailable, atlantoaxial instability was defined in the neutral position as an atlantodens interval of >4.0 mm in children one to eighteen years of age, >3.0 mm in adult men, and >2.5 mm in adult women⁹⁻¹¹. Subaxial instability was defined as translation of the C2-C7 posterior vertebral lines >3.5 mm from the neutral position during flexion or extension¹¹. When flexion and extension radiographs were unavailable, instability was defined as subluxation of C2-C7 >3.5 mm in the neutral position⁹⁻¹¹.

Fig. 2
Axial computed tomogram showing off-center odontoid (ratio of 0.34) in a nine-year-old girl without other cervical anomalies.

Statistical Analyses

Means and SDs were calculated with use of Microsoft Excel software. We used the Fisher exact test to determine the significance of the association between

type of TGF- β R mutation and cervical abnormalities and the Student *t* test to determine whether age at presentation was significantly associated with type of TGF- β R mutation. Significance was set at $p = 0.05$.

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Results

Vertebral Anomalies

Malformation of the upper-cervical vertebrae, particularly C1-C3, was common (sixty-one patients, 76%) (Table I, Fig. 3).

Anomalies of the Atlas

Twenty-eight patients (35%) had a malformed atlas. Anterior arch defects were present in nineteen (24%) and posterior arch defects, in thirteen (16%); nine (11%) had combined anterior and posterior arch defects. The mean age of patients with arch defects was thirteen years (range, three to forty-seven years). Five patients (6%) had hypoplasia of the lateral

Fig. 3
Prevalence of common cervical spine abnormalities in Loeys-Dietz syndrome.

Fig. 4-A

Fig. 4-B

Figs. 4-A through 4-D Lateral radiographs showing subaxial vertebral body hypoplasia across the age spectrum. **Fig. 4-A** Eight-month-old boy with C3 hypoplasia, resulting in focal kyphosis and subaxial instability, who demonstrated motor delay and weakness. Surgery was recommended because of kyphosis, instability, and likelihood of further neurologic compromise. However, treatment was delayed (with bracing) because of multiple cardiovascular procedures. **Fig. 4-B** Thirty-month-old boy with C3 hypoplasia, resulting in focal kyphosis and subaxial instability, who presented with apneic episodes and motor delay. Posterior spinal fusion was attempted at three months. However, this attempt did not allow fixation. He was managed with bracing until thirty months of age and then underwent posterior spinal fusion from the occiput to C4.

masses or atlas arch without fusion defects, with three having cervical malalignment.

Axial Anomalies

Fifty-three patients (66%) had malformation of C2; forty-three (54%) had dens elongation (see Appendix) (mean dens height, 3.0 ± 0.8 cm). Standards in the literature⁶ used for comparison included adults twenty to fifty years of age; most of our patients were younger than twenty years old, suggesting that the difference in dens height might be even greater if ages were matched. Of the twenty-five patients more than twenty years old, twenty (80%) had dens elongation. Fifteen of those twenty had radiographic evidence of basilar impression (mean distance from the tip of the odontoid above the McGregor line, 9.7 mm; range, 6.0 to 22.9 mm).

Twenty-six patients (33%) had radiographic evidence of basilar impression, but it was mild and asymptomatic in most (twenty patients). The mean projected distance from the tip of the odontoid to the McGregor line in asymptomatic and symptomatic patients was 8.5 mm (range, 6.0 to 13.6 mm) and 10.6 mm (range, 6.2 to 22.9 mm), respectively ($p = 0.3$). Among the six symptomatic patients, four had recurrent headaches and two had cervicomedullary junction crowding with symptoms of hypotonia and paresthesia. Those with cervicomedullary junction crowding had additional anomalies, including C1 hypoplasia (both patients) and apex-anterior angulation of the dens (one patient) (Figs. 1-A and 1-B).

Apex-anterior dens angulation was present in twelve patients (15%), three of whom experienced symptomatic cervicomedullary compression (Figs. 1-A and 1-B), manifesting apneic episodes, motor weakness, hypotonia, or upper and lower-extremity contractures.

Four patients (5%) had spondylolysis of C2 (mean age, four years; range, twenty months to twelve years). All four patients had subaxial instability and focal kyphosis of C2-C3 (indications for surgery). Clinical findings included apneic episodes in two, paresthesia in two, and head tilt in all.

The dens was off-center within the atlas ring in twenty-one patients (26%) (Fig. 2). In most, this finding did not have clinical importance; however, three patients did have atlanto-axial instability. The laxity of the C1-C2 joint capsules, abnormal development of the dens, and/or differences in the slopes of the C2 lateral masses may have caused the dens to align or appear in this way on CT.

Subaxial Anomalies

Ten patients (13%) had hypoplasia and anterior wedging of the subaxial cervical vertebrae (Figs. 4-A through 4-D, and see Appendix). The most commonly involved level was C3 (nine patients); three patients had hypoplasia of the C4 or C5 body. Patients with subaxial anomalies had cervical instability (two patients), focal kyphosis (one patient), or both (seven patients).

Fig. 4-C

Fig. 4-D

Twenty-three-year-old man with C4 hypoplasia resulting in focal kyphosis (**Fig. 4-C**) and sixty-year-old man with C3 hypoplasia resulting in focal kyphosis and subaxial instability (**Fig. 4-D**). Both of these patients had mild neck pain without other symptoms and did not require surgery.

Focal Cervical Kyphosis

Twelve patients (15%) had focal cervical kyphosis (mean magnitude, $33.7^\circ \pm 26.4^\circ$). The upper cervical spine was most commonly involved.

Eight of those patients also had cervical instability (Figs. 4-A through 4-D, and see Appendix); surgery was required by or recommended for six because of the kyphotic deformity, instability, symptoms, and the potential for further neurologic compromise.

Cervical Instability

Thirteen patients (16%) had cervical instability: atlantoaxial, eight (10%) and subaxial, nine (11%) (four patients had both). Of the thirteen patients, eleven had additional vertebral anomalies, including malformation or hypoplasia of the atlas (seven patients), dens abnormalities (eleven patients: four, elongation; one, apex-anterior angulation; four, spondylolysis; and two, migration into the foramen magnum), off-center odontoid (four patients), and subaxial vertebral hypoplasia or wedging (nine patients).

Treatment and Complications

Eight patients had undergone posterior spinal fusion for cervical instability as shown on flexion and extension radiographs (mean age, four years; range, three months to twelve years). Six underwent surgery before the age of three years, and two developed cervical instability in late childhood after previous

radiographic documentation of normal alignment (see Appendix). Of the eight patients, two had atlantoaxial instability, two had subaxial instability, and four had atlantoaxial and subaxial instability. All were symptomatic: motor delay (five), contractures (five), hypotonia (five), apneic episodes (four), and paresthesia (two). Six of the eight had spinal cord compression with signal abnormality on magnetic resonance imaging (MRI).

All eight patients had posterior fusion of the cervical spine; two had posterior and anterior fusion. Two patients eventually had occiput-to-lumbar fusion; one patient required occiput-to-sacral fusion because of substantial thoracic kyphosis, trunk weakness, and junctional kyphosis (see Appendix).

All eight patients had undergone posterior spinal fusion involving the occiput, although initial fusion procedures in two patients did not involve the occiput. One patient initially had undergone C2-C4 posterior fusion at thirty months of age and required three reoperations (including anterior spinal fusion and extension of the posterior construct from the occiput to T2) for pseudarthrosis and fixation failure. Another patient initially had undergone C2-C3 posterior fusion at eighteen months of age and required reoperation (extension to the occiput) for occipitocervical instability.

Seven of the eight patients experienced postoperative complications requiring reoperation: pseudarthrosis (five, four of whom also had failure of fixation), junctional kyphosis or instability (three; see Appendix), and occipital-cervical instability (one). These complications required thirteen reoperations.

TABLE I Prevalence of Cervical Vertebral Anomalies and Malalignment in Loeys-Dietz Syndrome (N = 80)

Parameter	No. (%) of Occurrences Overall
C1	
Anterior arch defects	19 (24)
Posterior arch defects	13 (16)
Anterior and posterior arch defects	9 (11)
General hypoplasia	5 (6)
C2	
Elongation	43 (54)
Radiographic basilar impression	26 (33)
Apex-anterior angulation of dens	12 (15)
Spondylolysis	4 (5)
Off-center location	21 (26)
Subaxial vertebrae	
Hypoplasia	10 (13)
Malalignment	
Focal kyphosis	12 (15)
Total cervical instability*	13 (16)
Atlantoaxial instability*	8 (10)
Subaxial instability*	9 (11)
Any cervical abnormality	61 (76)

*Cervical instability was categorized as atlantoaxial or subaxial instability; some patients are included in both categories.

TABLE II Cervical Spine Abnormalities by TGF- β R Mutation*

Parameter	No. (%) of TGF- β R1, N = 22	No. (%) of TGF- β R2, N = 58	P Value
C1			
Anterior arch defects	4 (18)	15 (26)	0.566
Posterior arch defects	2 (9)	11 (19)	0.498
Any fusion defect	5 (23)	18 (31)	0.585
General hypoplasia	2 (9)	3 (5)	0.612
C2			
Elongation	11 (50)	32 (55)	0.803
Radiographic basilar impression	5 (23)	21 (36)	0.296
Apex-anterior angulation of dens	5 (23)	7 (12)	0.295
Spondylolysis	1 (5)	3 (5)	1.0
Off-center location	3 (14)	18 (31)	0.158
Subaxial vertebrae			
Hypoplasia	1 (5)	9 (16)	0.270
Malalignment			
Focal kyphosis	2 (9)	10 (17)	0.495
Cervical instability†	2 (9)	11 (19)	0.498
Atlantoaxial instability†	1 (5)	7 (12)	0.434
Subaxial instability†	1 (5)	8 (14)	0.432
Any cervical abnormality	17 (77)	44 (76)	1.0

*TGF- β R = transforming growth factor-beta receptor. †Cervical instability was categorized as atlantoaxial or subaxial instability; some patients are included in both categories.

It is unclear why one patient did not experience postoperative complications; her age, levels of fusion, and duration of postoperative halo traction did not distinguish her from the other patients. Her initial fusion to the occiput, and stable fixation at the axis, may have provided better stability. The mean follow-up after surgery was six years (range, two to fourteen years).

Five of the eight patients were initially managed with bracing until definitive fusion could be performed (range of bracing, two weeks to twenty-seven months). Although bracing did not relieve clinical symptoms and radiographic deformity, it prevented further progression of the deformity and further neurologic deterioration in all eight patients. For example, in one patient, the initial attempt at surgical fusion at three months did not allow fixation intraoperatively (Fig. 4-B). This patient was therefore managed with bracing until successful fusion at thirty months.

Surgical fusion was recommended for a ninth patient (with subaxial instability) at seven months but was delayed because of cardiovascular procedures. At the time of writing, this patient had been braced for twenty-five months without deformity or neurologic progression.

Another patient was treated, at three years of age, for atlantoaxial rotatory instability with halo traction; successful correction was achieved after six weeks. After seven years, he had no radiographic or clinical evidence of cervical instability.

Statistical Results

Patients with mutations of TGF- β R1 and TGF- β R2 had similar distributions of cervical spine findings; however, the prevalence of most reported abnormalities was higher among the latter. Nevertheless, we found no significant association of TGF- β R type with specific cervical abnormalities (Table II) or age at presentation ($p = 0.632$).

Discussion

The TGF- β family of cytokines influences an array of cellular processes that are key in growth and development. These signaling pathways help regulate deposition of extracellular matrix and formation of vasculature, cartilage, and bone¹². Thus, disruptions in the TGF- β signaling pathways likely contribute to the abnormal bone morphology and ligamentous laxity found with Loeys-Dietz syndrome. Cervical spine malalignment and instability are among the many consequences of such primary osseous malformations and ligamentous laxity.

Mutations of TGF- β R1 account for approximately 20% of cases with Loeys-Dietz syndrome, whereas mutations in TGF- β R2 account for roughly 70% of cases; 10% are associated with mutations in SMAD3 and TGF- β 2¹³. We had no patient with a mutation of SMAD3 or TGF- β 2; although the prevalence of most cervical abnormalities was slightly higher in patients with TGF- β R2 mutations, the type of TGF- β receptor mutation (TGF- β R1 versus TGF- β R2) was not significantly associated with the presence of cervical vertebral anomalies or instability.

Atlas defects were common; they may follow the pattern of midline defects with Loeys-Dietz syndrome, including those

involving the palate, uvula, and cranial sutures. Midline fusion defects of the C1 arch occurred in 29% of our patients but occur much less frequently (2% to 4%) in the general population¹⁴⁻¹⁶. In addition, our patients had anterior arch defects more often than posterior arch defects; in the general population, posterior arch defects are typically 4.5 times more common^{16,17}. A previous study also found that fusion defects of the C1 arch are often asymptomatic and of no clinical importance except when associated with trauma or other occipital-cervical defects that promote instability, or when operative fusion is needed¹⁷. In our cohort, this observation remained true: all patients with atlas defects were asymptomatic except for those with additional vertebral anomalies leading to instability. General hypoplasia of the atlas seemed to be of greater consequence: three of the five patients with hypoplastic C1 had cervical malalignment, likely the result of disruption of the C1-C2 articulation.

Axial anomalies were also common. Of the patients with elongated dens, only one-third had radiographic evidence of basilar impression; most were asymptomatic. Dens migration into the foramen magnum and cervicomedullary junction compression were more often associated with apex-anterior dens angulation (three patients) and atlas hypoplasia (two patients) than with elongated dens (one patient).

Spondylolysis of C2 was associated with marked subaxial instability in all four affected patients; however, each patient also had hypoplastic subaxial vertebrae or facet joints and neurologic deficits. Spondylolysis of the cervical spine is rare, particularly at C2¹⁸. Gressot et al.¹⁸ recently analyzed ten such children with congenital spondylolysis of C2 and found that additional vertebral anomalies and neurologic deficits tended to be risk factors for the development of cervical instability necessitating surgery, consistent with our observations.

Subaxial vertebral hypoplasia was associated with focal kyphosis and subaxial instability. Most often, C3 was hypoplastic, creating a substantial kyphotic deformity at C2-C3 and anterior subluxation of C2 over C3 (Figs. 4-A through 4-D, and see Appendix). It is not known whether the C3 hypoplasia or the instability occurs first. However, it seems most plausible that the C3 hypoplasia is a developmental deformity resulting from the laxity of the C2-C3 articulation, especially in patients with axial spondylolysis. This deformity and instability pattern was present in seven patients; all but one had neurologic sequelae. Such vertebral hypoplasia and midcervical kyphosis are prominent features in other genetic syndromes, including Larsen syndrome and diastrophic dysplasia¹⁹. The kyphotic deformities observed in Loeys-Dietz syndrome, however, appear to be more focal and cephalad than in those other two syndromes¹⁹⁻²². Focal kyphosis has also been reported in 16% of patients with Marfan syndrome⁷; however, that study did not report associated subaxial vertebral hypoplasia or malformation⁷, and some of the patients may have had unrecognized Loeys-Dietz syndrome.

Cervical instability presented in childhood (most often by three years of age) in all but one patient. Most had neurologic deficits that prompted evaluation for cervical instability. Despite this pattern, there were a few exceptions. One patient (see Appendix) with normal cervical alignment on imaging in

early childhood developed symptomatic C2-C3 subluxation at twelve years of age. Another patient had normal cervical alignment on routine surveillance imaging at age eight but, at age nine, developed C1-C2 flexion instability requiring occiput-to-C2 posterior fusion. A third patient (Fig. 4-D) was sixty years old before being diagnosed with atlantoaxial and subaxial instability on radiographs for neck pain. Considering these examples and the potential morbidity associated with cervical instability, we recommend screening for cervical instability using flexion and extension radiographs on initial diagnosis of Loeys-Dietz syndrome. We also recommend periodic surveillance imaging of the cervical spine, particularly if new neurologic symptoms develop or if general endotracheal anesthesia is required.

Many patients who had undergone surgical fusion for cervical instability were initially managed with bracing until their vertebrae were deemed large enough for adequate fixation. Bracing was used for fourteen months in one patient and for more than two years in two patients; no patient had substantial deformity progression. Therefore, bracing seems a reasonable bridge to delaying definitive surgical management.

All patients who had undergone surgical fusion had posterior approaches (two also had anterior procedures) and ultimately required posterior fusion to the occiput for adequate fixation. The surgical approaches and postoperative complications in our cohort reflect the bone fragility previously reported in Loeys-Dietz syndrome²³⁻²⁵. Although it is unclear specifically how aberrant TGF- β signaling affects bone development, it is speculated that it causes uncoupling of bone formation and resorption^{25,26}. Pseudarthrosis and failure of fixation were particularly common complications and may reflect defects in bone mineralization and resorption²⁵. Other common postoperative complications, including junctional kyphosis and instability, are likely the result of ligamentous laxity. Surgeons should anticipate difficulty in obtaining rigid fixation and consider anterior fusion or postoperative external support.

The difficulty in obtaining successful fusion seems related to the quality of the internal fixation, leading us to suggest that very young children with deformity but no neurologic deficit may be best managed with observation or bracing until clinically notable progression occurs or the surgeon can achieve rigid fixation as judged by imaging. Because of the frequency of spondylolysis and other anomalies, CT may be needed to determine the levels and method of fixation. Selection of end vertebrae that allow stable fixation, use of appropriately sized instrumentation, autologous bone graft, and postoperative halo immobilization may lessen the reported high complication rate.

Our study had several limitations. Our institution is a referral center for patients with Loeys-Dietz syndrome, so we may have seen more severely involved patients. We attempted to reduce sampling bias by using genetics records from our institution rather than orthopaedic records alone. However, cervical imaging was not available for all patients; presumably those with cervical imaging had more cervical involvement. Also, many patients were children who may have yet to develop signs or symptoms of instability. Conversely, none of the adults had childhood records, so it is unclear whether they may have previously had malalignment that resolved.

In conclusion, cervical osseous deformity (most often C1-C3) and instability are common in Loeys-Dietz syndrome. Many primary osseous deformities, including C1 fusion defects, C2 elongation, and off-center C2 location, seem of limited clinical importance. Other vertebral anomalies, including hypoplasia of C1, spondylolysis of C2, and subaxial hypoplasia may lead to malalignment, particularly if other osseous anomalies are present. Hypoplasia of C3 often is associated with a pattern of C2-C3 focal kyphosis and subaxial instability. Surgical treatment for instability and focal kyphosis is indicated if neurologic signs and focal kyphosis are progressing despite adequate bracing. Postoperative complications are frequent because of increased bone fragility and altered shape. Imaging surveillance is recommended at diagnosis and at onset of symptoms related to the cervical spine.

Appendix

Radiographic, CT, and magnetic resonance images of two pediatric patients, with summaries of their surgical management, and a CT image of one adult patient are available with the online version of this article as a data supplement at jbjs.org. ■

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References

- Loeys BL, Chen J, Neptune ER, Judge DP, Podowski M, Holm T, Meyers J, Leitch CC, Katsanis N, Sharifi N, Xu FL, Myers LA, Spevak PJ, Cameron DE, De Backer J, Hellemans J, Chen Y, Davis EC, Webb CL, Kress W, Coucke P, Rifkin DB, De Paepe AM, Dietz HC. A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. *Nat Genet.* 2005 Mar;37(3):275-81. Epub 2005 Jan 30.
- Erkula G, Sponseller PD, Paulsen LC, Oswald GL, Loeys BL, Dietz HC. Musculoskeletal findings of Loeys-Dietz syndrome. *J Bone Joint Surg Am.* 2010 Aug 4; 92(9):1876-83.
- Loeys BL, Schwarze U, Holm T, Callewaert BL, Thomas GH, Pannu H, De Backer JF, Oswald GL, Symoens S, Manouvrier S, Roberts AE, Faravelli F, Greco MA, Pyeritz RE, Milewicz DM, Coucke PJ, Cameron DE, Braverman AC, Byers PH, De Paepe AM, Dietz HC. Aneurysm syndromes caused by mutations in the TGF-beta receptor. *N Engl J Med.* 2006 Aug 24;355(8):788-98.
- Sousa SB, Lambot-Juhan K, Rio M, Baujat G, Topouchian V, Hanna N, Le Merrer M, Brunelle F, Munnich A, Boileau C, Cormier-Daire V. Expanding the skeletal phenotype of Loeys-Dietz syndrome. *Am J Med Genet A.* 2011 May;155A(5):1178-83. Epub 2011 Apr 11.

5. Williams JA, Loeys BL, Nwakanma LU, Dietz HC, Spevak PJ, Patel ND, François K, DeBacker J, Gott VL, Vricella LA, Cameron DE. Early surgical experience with Loeys-Dietz: a new syndrome of aggressive thoracic aortic aneurysm disease. *Ann Thorac Surg*. 2007 Feb;83(2):S757-63: discussion S785-90.
6. Schaffler MB, Alson MD, Heller JG, Garfin SR. Morphology of the dens. A quantitative study. *Spine (Phila Pa 1976)*. 1992 Jul;17(7):738-43.
7. Hobbs WR, Sponseller PD, Weiss APC, Pyeritz RE. The cervical spine in Marfan syndrome. *Spine (Phila Pa 1976)*. 1997 May 1;22(9):983-9.
8. McGregor M. The significance of certain measurements of the skull in the diagnosis of basilar impression. *Br J Radiol*. 1948 Apr;21(244):171-81.
9. Hinck VC, Hopkins CE. Measurement of the atlanto-dental interval in the adult. *Am J Roentgenol Radium Ther Nucl Med*. 1960 Nov;84(5):945-51.
10. Locke GR, Gardner JI, Van Epps EF. Atlas-dens interval (ADI) in children: a survey based on 200 normal cervical spines. *Am J Roentgenol Radium Ther Nucl Med*. 1966 May;97(1):135-40.
11. White AA 3rd, Johnson RM, Panjabi MM, Southwick WO. Biomechanical analysis of clinical stability in the cervical spine. *Clin Orthop Relat Res*. 1975;(109):85-96.
12. Cohen MM Jr. TGF beta/Smad signaling system and its pathologic correlates. *Am J Med Genet A*. 2003 Jan 1;116(1):1-10.
13. Loeys BL, Dietz HC. Loeys-Dietz syndrome. Pagon, RA, Adam, MP, Ardinger, HH, Bird, TD, Dolan, CR, Fong, CT, Smith, RJH, Stephens, K, editors. *GeneReviews* [Internet]. 1993. <http://www.ncbi.nlm.nih.gov/books/NBK1133/>. Accessed 2014 Apr 17.
14. Petre BM, Karp JE, Riley LH 3rd. Athletic cervical spine injury in the setting of fusion failure of the anterior and posterior atlas. *Orthopedics*. 2012 Sep;35(9):e1449-52.
15. Piatt JH Jr, Grissom LE. Developmental anatomy of the atlas and axis in childhood by computed tomography. *J Neurosurg Pediatr*. 2011 Sep;8(3):235-43.
16. Senoglu M, Safavi-Abbasi S, Theodore N, Bambakidis NC, Crawford NR, Sonntag VKH. The frequency and clinical significance of congenital defects of the posterior and anterior arch of the atlas. *J Neurosurg Spine*. 2007 Oct;7(4):399-402.
17. Sherk HH. Lesions of the atlas and axis. *Clin Orthop Relat Res*. 1975;(109):33-41.
18. Gressot LV, Vadivelu S, Hwang SW, Fulkerson DH, Luerssen TG, Jea A. Spondylolysis of C-2 in children 3 years of age or younger: clinical presentation, radiographic findings, management, and outcomes with a minimum 12-month follow-up. *J Neurosurg Pediatr*. 2014 Feb;13(2):196-203. Epub 2013 Dec 20.
19. McKay SD, Al-Omari A, Tomlinson LA, Dormans JP. Review of cervical spine anomalies in genetic syndromes. *Spine (Phila Pa 1976)*. 2012 Mar 1;37(5):E269-77.
20. Johnston CE 2nd, Birch JG, Daniels JL. Cervical kyphosis in patients who have Larsen syndrome. *J Bone Joint Surg Am*. 1996 Apr;78(4):538-45.
21. Poussa M, Merikanto J, Ryöppy S, Marttinen E, Kaitila I. The spine in diastrophic dysplasia. *Spine (Phila Pa 1976)*. 1991 Aug;16(8):881-7.
22. Remes VM, Marttinen EJ, Poussa MS, Helenius IJ, Peltonen JI. Cervical spine in patients with diastrophic dysplasia—radiographic findings in 122 patients. *Pediatr Radiol*. 2002 Sep;32(9):621-8. Epub 2002 Jul 4.
23. Ben Amor IM, Edouard T, Glorieux FH, Chabot G, Tischkowitz M, Roschger P, Klaushofer K, Rauch F. Low bone mass and high material bone density in two patients with Loeys-Dietz syndrome caused by transforming growth factor beta receptor 2 mutations. *J Bone Miner Res*. 2012 Mar;27(3):713-8.
24. Kirmani S, Tebben PJ, Lteif AN, Gordon D, Clarke BL, Hefferan TE, Yaszemski MJ, McGrann PS, Lindor NM, Ellison JW. Germline TGF-beta receptor mutations and skeletal fragility: a report on two patients with Loeys-Dietz syndrome. *Am J Med Genet A*. 2010 Apr;152(4):1016-9.
25. Tan EW, Offhoh RU, Oswald GL, Skolasky RL, Dewan AK, Zhen G, Shapiro JR, Dietz HC, Cao X, Sponseller PD. Increased fracture risk and low bone mineral density in patients with Loeys-Dietz syndrome. *Am J Med Genet A*. 2013 Aug;161(8):1910-4. Epub 2013 Jul 4.
26. Tang Y, Wu X, Lei W, Pang L, Wan C, Shi Z, Zhao L, Nagy TR, Peng X, Hu J, Feng X, Van Hul W, Wan M, Cao X. TGF-beta1-induced migration of bone mesenchymal stem cells couples bone resorption with formation. *Nat Med*. 2009 Jul;15(7):757-65. Epub 2009 Jul 5.