Neurosurgical Management of Lateral Meningocele Syndrome: A Clinical Update for the Pediatric Neurosurgeon

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Keywords

Lateral meningocele syndrome · Lehman syndrome · Marfan syndrome · Ehlers-Danlos syndrome · Loeys-Dietz syndrome

Abstract

Background: Lateral meningocele syndrome (LMS) is an exceedingly rare connective tissue disease with phenotypic anomalies similar to those seen in Marfan syndrome, Ehlers-Danlos syndrome, and Loeys-Dietz syndrome. However, this syndrome is invariably associated with the presence of multiple lateral thoracolumbar spinal meningoceles: a distinct point of phenotypic divergence from other connective tissue disorders. The etiopathogenesis of this syndrome has recently been linked to truncating mutations within exon 33 of *NOTCH3*. Despite numerous reports, neurosurgical management of multiple spinal meningoceles remains poorly defined in the literature. We conducted a literature review to provide insight into the nosology, clinical significance, and neurosurgical management strategies of this distinct connective tissue disorder. **Summary:** Our literature search revealed 11 articles (16 cases) of LMS, which included 9 males

and 7 females, belonging to 14 different families. Half of these cases underwent genetic screening: all of which were discovered to exhibit a truncating mutation within exon 33 of *NOTCH3*. All patients exhibited multiple lateral thoracolumbar spinal meningoceles with craniofacial dysmorphisms. Other clinical characteristics included pathologic changes in spine morphology, Chiari I malformation, syringomyelia, hydrocephalus, and tethered cord. Operative management of multiple spinal meningoceles in LMS is complicated by the presence of such coexisting structural neurologic pathologies, which may alter cerebrospinal fluid flow dynamics and, ultimately, impact operative intervention. **Key Messages:** LMS is an exceedingly rare connective tissue disorder with severe spinal dural involvement. Neurosurgical management of multiple spinal meningoceles is complex, which is further complicated by the presence of coexisting neuropathology, such as pathologic transformation of spine morphology and Chiari I malformation. Patients with a connective tissue disorder phenotype found to have multiple spinal meningoceles on imaging studies may benefit from evaluation by a medical geneticist and a pediatric neurosurgeon.

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Introduction

Notch receptors are highly conserved transmembrane glycoproteins that regulate numerous cellular functions, such as cell differentiation, self-renewal, proliferation, and survival [1–6]. Notch3 expression is found in a variety of tissues, such as vascular smooth muscle and skeletal cells, among others [7–15]. Exome sequencing of *NOTCH3* has identified several novel diseases restricted to specific exons on chromosome 19p13 including cerebral arteriopathy autosomal dominant with subcortical infarcts and the recently described clinical entity known as lateral meningocele syndrome (LMS) [16–19]. The clinical significance of physiologic Notch3 can be grossly appreciated in individuals who exhibit a truncation mutation of exon 33 in *NOTCH3*. Indeed, the pleiotropic effects of a truncated *NOTCH3* gene product are vast. Patients with LMS invariably exhibit multiple lateral thoracolumbar spinal meningoceles as well as varying degrees of craniofacial dysmorphisms, musculoskeletal, and soft tissue anomalies (Fig. 1, 2). Several connective tissue disorders exhibit an overlapping phenotype with LMS and include some degree of dural pathology. For example, lumbosacral dural ectasia has been documented as a phenotypic feature of Marfan syndrome, Loeys-Dietz syndrome, and Nevo syndrome [20–22]. Moreover, single-level thoracic meningoceles and lumbosacral Tarlov's cysts are known to be associated with neurofibromatosis type I and Ehler-Danlos syndrome, respectively [23, 24]. Nevertheless, LMS is now classified as a novel entity associated with a specific subset of mutations in exon 33 of *NOTCH3*. To date, only 16 cases of LMS have been reported, of which 8 cases have been confirmed via exome sequencing (Table 1) [18, 25–34]. Here, we provide a literature review of LMS encompassing the history of the disease from first observation to genetic classification, clinical significance, and neurosurgical management approaches.

First Observation to Genetic Classification

In 1977, Lehman et al. [25] first reported a mother and daughter with similar phenotypic features including craniofacial dysmorphisms, skeletal sclerosis, and multiple lateral spinal meningoceles. Pyknodysostosis was considered as a potential diagnosis; however, these patients demonstrated anomalies not previously reported in pyknodysostosis, such as basilar invagination, platybasia, enlargement of the foramen magnum and sella turcica,

posterior scalloping of the vertebral bodies, spinal canal widening, and, importantly, spinal meningoceles [25]. One year later, Katz et al. [26] described a similar case in a 2-year-old male with multiple paraspinal masses and a widened spinal canal who initially presented for evaluation for failure to thrive. In 1995, Philip et al. [27] described a 19-year-old male with strikingly similar features to the 2 patients previously reported by Lehman et al. [25] including identical spinal anomalies and similar craniofacial dysmorphisms. The main distinction between these 2 reports was degree of bone density. Nevertheless, Philip et al. [27] suggested an autosomal dominant inheritance pattern as mode of genetic transmission, suggested by maternal transmission in Lehman's case and advanced paternal age in their report [25]. In 1997, Gripp et al. [28] reported novel phenotypic characteristics of the syndrome including a Chiari I malformation, syringomyelia, congenital cardiovascular anomalies (i.e., patient ductus arteriosus, enlarged aortic root), pectus deformity, and joint hypermobility. The authors suggested renaming this clinical entity as LMS to emphasize the most consistent and unique finding in these patients. Chen et al. [29] described 3 additional patients including an affected mother and daughter pair further suggesting an autosomal dominant pattern of inheritance. Avela et al. [30] reported a case of Hajdu-Cheney syndrome with spinal meningoceles; however, this case was later reclassified as LMS after genetic sequencing confirmed a *NOTCH3* mutation in exon 33 [35]. Lateral spinal meningoceles extending into the sacral spine was first described by Alves et al. [31]. The authors also reported the same patient to exhibit a novel cardiac anomaly with a bicuspid aortic valve. In 2014, Castori et al. [32] described the features of LMS in a 55-year-old female: the oldest patient to be diagnosed with LMS to date. Remarkably, this patient was reported to exhibit multiple lateral meningoceles within the cervical, thoracolumbar, and sacral spine. Notably, all cases reported up until this point in time were classified as LMS based solely on phenotypic description: the etiopathogenesis of LMS was not discovered until 2015.

In 2015, Gripp et al. [18] performed whole-exome sequencing and/or Sanger sequencing in 6 unrelated individuals diagnosed with LMS based on phenotypic description. These 6 individuals included one newly described case and 5 previously reported cases (Patients 1 and 2 of Gripp et al. [28], Patient 3 of Chen et al. [29], Patient 1 of Avela et al. [30], and Patient 1 of Alves et al. [31]) [18]. The authors reported 5 novel de novo *NOTCH3* mutations in 6 unrelated patients [18]. All mutations

Fig. 1. T2 magnetic resonance imaging of the spine in a lateral meningeal syndrome patient. **a** Sagittal and **(b)** axial views demonstrate numerous lateral meningoceles protruding through the thoracolumbar foramina. Adapted from Ejaz et al. [33]. GeneReviews [Internet]; 2016. ©1993–2019 University of Washington. GeneReviews® is a registered trademark of the University of Washington, Seattle. The content is used with permission. All rights reserved.

were de novo and found to be within the last coding exon of the gene, exon 33. Subsequently, 2 additional cases of LMS were described, each with a novel de novo *NOTCH3* mutation within exon 33 [33, 34].

Clinical Significance

Our literature search revealed 11 articles of LMS describing 16 patients, 9 males and 7 females, belonging to 14 different families [18, 25–34]. The average age at diagnosis was 11.7 years (range 6 months – 55 years old; median 6 years old). Fifty-percent of these cases underwent genetic screening; all of which were discovered to exhibit a truncating *NOTCH3* mutation in exon 33 [18]. The pleiotropic manifestations of a truncated *NOTCH3* gene product are vast. Our literature review documented the presence of multiorgan pathology including central and peripheral nervous system anomalies, craniofacial dysmorphisms, and soft tissue anomalies. All currently described cases of LMS exhibit multiple lateral meningoceles within the thoracolumbar spine [18, 25–34]. In addition to the thoracolumbar spine, meningoceles in LMS patients have been reported to extend to the sacrum in one report and to include the entire spine in another [31, 32]. Other common structural neurologic anomalies described included a widened spinal canal (81.3%), scalloped vertebrae (75.0%), and scoliosis (56.3%). Interestingly, there seems to be a higher prevalence of Chiari I

malformation (25.0%) in LMS patients compared to the general population (0.1%). The majority of LMS patients exhibit a functional neurologic deficit, such as hypotonia (75.0%) and/or developmental delay (50.0%). Craniofacial dysmorphic features were reported in all cases with the majority of patients exhibiting micro- or retrognathia (93.8%), angulated ears (87.5%), eyelid ptosis (81.3%), downslanting palpebral fissures (81.3%), high arched palate (75.0%), and hypertelorism (62.5%). Additionally, commonly described soft tissue anomalies included cryptorchidism in males (6 of 9 male patients) and joint hypermobility (62.5%). As depicted by the broad phenotype of LMS, *NOTCH3* truncation mutations within exon 33 have extensive implications on systems biology.

Hereditary connective tissue diseases share similar features with LMS including spinal dural pathology. The most distinctive characteristic of LMS is multiple lateral spinal meningoceles herniating through the spinal foramina with associated scalloping of the posterior aspect of the vertebral body and widening of the spinal canal. This feature occurs predominantly in a gravity-dependent manner with meningoceles typically found in the lower thoracic and lumbar spine unlike neurofibromatosis type I where such lesions more commonly occur in the thoracic spine [23]. Moreover, it is known that lumbosacral dural ectasia is a feature of Marfan syndrome, Loeys-Dietz syndrome, and Nevo syndrome, whereas lumbosacral Tarlov's cysts are known to be associated

Fig. 2. Phenotypic representation of individuals diagnosed with LMS. **a, b** Individual at the age of 24 years with facial characteristics including eyelid ptosis, arched eyebrows, a thin upper lip, and angulated ears. **c, d** Same individual with pseudoclubbing of the second and third digits. **e** Individual at the age of 13 years with facial characteristics including eyelid ptosis, arched eyebrows, a thin upper lip, angulated ears, coarse hair, and micrognathia. **f, g** Same individuals at the age of 4 years with similar facial features. **h, i** Individual at the age of 6 years with facial characteristics including eyelid ptosis, arched eyebrows, a thin upper lip, angulated eyes, and flattening of the midface. Adapted from Ejaz et al. [33] Lateral meningocele syndrome. GeneReviews [Internet]; 2016. ©1993–2019 University of Washington. GeneReviews® is a registered trademark of the University of Washington, Seattle. The content is used with permission. All rights reserved.

with Ehler-Danlos syndrome [20–22, 24]. Common phenotypic features shared between LMS and such connective tissue diseases include micro- or retrognathia, angulated ears, eyelid ptosis, high or cleft palate, hypertelorism, and dolicocephaly as well as hyperextendable joints and muscular hypotonia [20–22, 24]. However, each connective disorder sharing overlapping features with LMS exhibits specific mutation loci outside of the *NOTCH* genes with the exception of Hajdu-Cheney syndrome [21, 36].

Hajdu-Cheney syndrome is a rare connective tissue disorder with overlapping clinical characteristics seen in LMS. However, *NOTCH2* mutations are associated with Hajdu-Cheney syndrome [30, 36]. Similar to the etio-pathogenesis of LMS, *NOTCH2* mutations in Hajdu-Cheney syndrome cluster to the last exon and are predicted to result in a truncated gene product [30, 36]. The effects of this aberrant protein have been linked to the phenotype typically seen in Hajdu-Cheney syndrome consisting of a thickened occiput, wormian bones, micro-

Table 1. Phenotypic description and clinical symptomatology of LMS patients

Features	Lehman et al. [25]		Katz et al. [26]	Philip et al. [27]	Gripp et al. [28]			Chen et al. [29]			Avela et al. [30]	Alves et al. [31]	Castori et al. [32]	Gripp et al. [18]	Ejaz et al. [33]	Brown et al. [34]	Total, %
	Pt 1	Pt 2	Pt 1	Pt 1	Pt 1	Pt 2	Pt 3	Pt 1	Pt 2	Pt 3	Pt 1	Pt 1	Pt 1	Pt 1	Pt 1	Pt 1	
Age, years	14 y/o	NR	2 y/o	19 y/o	28 m/o	8 y/o	9 y/o	12 y/o	33 y/o	2 y/o	6 y/o	5 y/o	55 y/o	5 y/o	32 m/o	6 m/o	
Gender	F	F	M	M	M	M	F	F	F	M	M	M	F	M	M	F	
<i>NOTCH3</i> mutation	NR	NR	NR	NR	Single bp insertion	26 bp deletion	NR	NR	NR	Nonsense point mutation	De novo	Nonsense point mutation	NR	Nonsense point mutation	80 bp deletion	2 bp deletion	
Inheritance	NR	NR	NR	NR	De novo	De novo	NR	NR	NR	De novo	De novo	De novo	NR	De novo	De novo	De novo	
Structural neurologic																	
Spinal meningoceles	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Wide spinal canal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	81.3
Scalloped vertebrae	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	75.0
Scoliosis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	56.3
Cranial hyperostosis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	25.0
Enlarged sella	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	25.0
Chiari I malformation	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	25.0
Syringomyelia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	18.8
Abnormal C1	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	18.8
Platybasia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	12.5
Enlarged foramen magnum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	12.5
Cranial encephalocle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	6.3
Cerebellar malformation	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	6.3
Hydrocephalus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	6.3
Tethered cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	6.3
Functional neurologic																	
Hypotonia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	75.0
Developmental delay	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50.0
Hearing loss	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43.8
Weakness	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	31.3
Sensory neuropathy	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	18.8
Incontinence	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	12.5
Intellectual disability	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	6.3
Craniofacial																	
Micrognathia/retrognathia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	93.8
Angulated ears	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	87.5
Eyelid ptosis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	81.3
Downslanting palpebral fissures	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	81.3
High arched palate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	75.0
Hypertelorism	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	62.5
Dolichocephaly/bossing	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43.8
Dental crowding	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43.8
Ocular proptosis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	31.3
Cleft palate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	25.0
Epicanthic folds	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	25.0
Coarse hair	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	18.8
Short neck	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	18.8
Others																	
Cryptorchidism	N/A	N/A	+	+	+	+	N/A	N/A	N/A	+	+	+	N/A	+	+	N/A	66.6
Joint hypermobility	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	62.5
Short stature	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43.8
Pectus deformity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	37.5
Congenital cardiac anomaly	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	31.3
Wormian bones	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	31.3
Inguinal hernia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	25.0
Skin hyperextensibility	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	12.5
Osteoporosis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	12.5

LMS, lateral meningocele syndrome; Pt, patient; y/o, years old; m/o, months old; F, female; M, male; NR, not reported; bp, base pair; T, thoracic; L, lumbar; S, sacral; C, cervical; N/A, not applicable.

Table 2. Summary of neurosurgical management strategies in LMS patients

Author/ Reference	Year	Age at diagnosis	Gender	Preoperative diagnosis	Preoperative symptoms/ indications	Procedure	Postoperative complications	Outcome
Lehman et al. [25]	1977	14 y/o	F	T7–L4 meningoceles	Weakness, hypotonia, sensory neuropathy, ataxia	T7–9 laminotomies, opening of T7–9 arachnoid passages extending into meningocele, opening of dorsal meningocele	NR	Improvement in all preoperative deficits at 2-year follow-up
Philip et al. [27]	1995	19 y/o	M	Thoracolumbar meningoceles	Back pain, weakness	L1–2 laminectomy for lumboperitoneal shunt implantation	NR	Partial resolution of back pain at 6-month follow-up
Gripp et al. [28]	1997	28 m/o (Patient 1)	M	1 Thoracolumbar meningoceles, hydrocephalus 2a Chiari I, cervical syrinx 2b Pleural effusion 3 Abnormal C1	1 Hydrocephalus 2a Dysphagia, sleep apnea 2b Pleural effusion 3 Cervicomedullary instability	1 VPS 2a Suboccipital decompression, thoracic laminectomy with meningocele-pleural shunt 2b Diversion of distal catheter from pleura to peritoneum 3 Occiput–C2 fusion	1 NR 2a Pleural effusion 2b NR 3 NR	1 Improvement in motor development at 5-month follow-up 2a NR 2b NR 3 NR
Avela et al. [30]	2011	8 y/o (Patient 2)	M	Thoracolumbar meningoceles, kyphoscoliosis	Progressive kyphoscoliosis	Anterior-posterior T1–L3 fusion with fenestration of thoracic meningocele	NR	Improvement in scoliosis
		9 y/o (Patient 3)	F	T11–L5 meningoceles	NR	Lumboperitoneal shunt	NR	Improvement in irritability, decrease size of meningoceles
Castori et al. [32]	2014	55 y/o	F	Cervical, thoracolumbar, sacral meningoceles	Back pain	Correction of meningeal protrusions (unspecified)	Bowel/bladder incontinence, weakness	Wheelchair bound
Gripp et al. [18]	2015	5 y/o	M	1 Thoracolumbar meningoceles, tethered cord 2 Retethered cord	1 Acute onset low back pain, bowel/bladder incontinence, ataxia 2 NR	1 Release of tethered cord 2 Release of tethered cord	1 NR 2 NR	1 Resolution of ataxia and urinary incontinence with persistent bowel incontinence 2 Persistent urinary incontinence with neuropathic pain
Brown et al. [34]	2017	6 m/o	F	1 Thoracolumbar meningoceles, Chiari I 2 Interval expansion of meningoceles, macrocephaly	1 Dysphagia, choking episodes, aspiration 2 Irritability	1 ETV, suboccipital craniectomy, C1–3 laminectomies, tonsillar coagulation, expansive duraplasty 2 VPS	1 NR 2 NR	1 Improvement in preoperative symptoms at 2-week follow-up but with irritability at 5–6-week follow-up 2 Resolution of irritability, normalization of head circumference

LMS, lateral meningocele syndrome; y/o, years old; F, female; T, thoracic; L, lumbar; NR, not reported; M, male; m/o, months old; C, cervical; VPS, ventriculoperitoneal shunt; ETV, endoscopic third ventriculostomy.

gnathia, joint hypermobility, and acro-osteolysis [30, 36]. Importantly, no form of ductal ectasia has been documented in cases of Hajdu-Cheney syndrome: a distinct point of phenotypic divergence between these 2 syndromes.

Neurosurgical Management

Indications for operative intervention in LMS remain unclear. Several reports have advocated for surgical intervention in patients who develop symptomatology related to meningocele mass effect; however, such reports do not discuss the specific symptoms or findings that would warrant intervention nor do they comment on optimal timing of intervention [26, 29, 31]. Moreover, neurosurgical operative management of multiple spinal meningoceles is poorly defined in the literature. Kim et al. [37] recommended laminectomy in cases of a small single thoracic meningocele or costotransversectomy for larger lesions. The authors described a single large thoracic (T4) meningocele adherent to the pleura for which a transthoracic thoracotomy was performed with preoperative lumbar puncture for cyst decompression [37]. Rainov et al. [38] recommended laminectomy and ligation of single thoracic or lumbar meningoceles; however, the authors stated that multiple meningoceles with large dural connections cannot be treated by surgical means. Indeed, there are currently no defined operative methods to address the presence of multiple, broad-based spinal meningoceles in any context.

Operative management of multiple spinal meningoceles in LMS is complicated by the presence of coexisting structural neurologic pathologies in these individuals, such as Chiari I malformation, syringomyelia, hydrocephalus, scoliosis, or tethered cord, which may alter the flow dynamics of cerebrospinal fluid. Such aberrations in cerebrospinal fluid flow dynamics are evident in individuals with Chiari I malformations, whereby an increase in systolic cerebrospinal flow duration within the ventral spinal subarachnoid space results in syringogenesis [39]. Surgical options for Chiari I malformations with or without syringomyelia range from posterior fossa decompression to drainage of the syrinx cavity; however, direct drainage is not recommended as a first-line treatment as long-term outcomes have proven to be unfavorable [40]. The primary surgical option for Chiari I malformations with or without syringomyelia is posterior fossa decompression via suboccipital bone decompression with or without C1 laminectomy, dural opening, duraplasty, and

cerebellar tonsillar coagulation. This procedure aims to increase volumetric space, reduce pressure, and ultimately improve cerebrospinal flow at the level of the foramen magnum. Other considerations to account for prior to posterior fossa decompression include concomitant anterior compression of the brainstem, craniocervical bone anomalies, or hydrocephalus. Posterior occipital cervical fusion should be considered in cases with associated anterior compression of the brainstem or craniocervical bone pathology as posterior fossa decompression alone may result in the progression of preoperative symptomatology. Moreover, hydrocephalus should be addressed with cerebrospinal fluid diversion prior to considering posterior fossa decompression. Last, syrinx to subarachnoid shunting may be considered for Chiari I malformation with syringomyelia when posterior fossa decompression fails to cease syrinx progression [41].

Although the majority of reported cases of LMS have undergone some form of neurosurgical intervention to address spinal meningocele or their sequelae, operative details and management strategies of these cases are poorly described (Table 2). In 1977, Lehman et al. [25] performed the first operative intervention in an attempt to relieve symptomatology associated with thoracolumbar meningoceles. The surgery entailed T7–9 osteoplastic laminotomies, opening of T7–9 arachnoid passages extending into the meningoceles and fenestration of a large dorsal meningocele. The patient demonstrated an improvement in preoperative weakness, hypotonia, sensory deficits, and ataxia at 2-year follow-up. Philip et al. [27] described a L1–2 laminectomy for lumboperitoneal shunt implantation, which partially resolved the patient's low back pain at 6-month follow-up. Gripp et al. [28] described a complex surgical case of LMS with a coexisting Chiari I malformation, cervical syrinx, and hydrocephalus. A ventriculoperitoneal shunt was placed at 11 months old with an improvement in motor development at 5-month follow-up. At 22 months old the patient developed progressive sleep apnea and dysphagia, which was attributed to symptomatic progression of her Chiari I malformation. The patient underwent suboccipital decompression with a thoracic laminectomy and meningocele-pleural shunt. Subsequently, the patient developed a pleural effusion requiring conversion of the meningocele-pleural shunt to a meningocele-peritoneal shunt. At 23 months old, an occiput-C2 fusion was performed for cervicomedullary instability and abnormally formed C1. Gripp et al. [28] also described a case of LMS with progressive kyphoscoliosis where an anterior-posterior T1–L3 fusion was performed with fenestration of a large tho-

racic cyst. Castori et al. [32] reported a 55-year-old female with lateral meningoceles of the entire spine and chronic low back pain who underwent surgical correction of her meningoceles. Unfortunately, the patient suffered irreversible nerve damage with bladder and anorectal dysfunction as well as lower extremity weakness from the procedure. Gripp et al. [18] described a case of LMS found to have a tethered cord. The patient underwent surgical release of the cord with symptomatic improvement but ultimately retethered requiring a second surgery.

Recently, Brown et al. [34] described a complicated case of LMS with a severe Chiari I malformation, ventriculomegaly, and macrocephaly. The author described a 6-month-old female with progressive dysphagia and choking episodes [34]. Aggressive neurosurgical intervention was performed including an endoscopic third ventriculostomy, suboccipital craniectomy, C1–3 laminectomies, tonsillar coagulation, and extensive duraplasty at 7.5 months of age. The authors commented that an endoscopic third ventriculostomy was performed as an attempt to relieve the patient's ventriculomegaly and macrocephaly while simultaneously avoiding the potential long-term complications associated with ventriculoperitoneal shunt placement. The patient's preoperative symptoms improved at 2-week follow-up; however, at 5–6 week follow-up her parents noticed the patient becoming increasingly irritable with a right leg preference. Repeat magnetic resonance imaging demonstrated interval enlargement of her thoracic and lumbar meningoceles. As such, at 10.5 months of age, a ventriculoperitoneal shunt was placed in an attempt to reduce her cerebrospinal fluid burden and alleviate her new onset symptomatology. Clinical follow-up 2 weeks later revealed resolution of her irritability and full strength in her lower extremities.

Although there are no standard operative interventions to address multiple spinal meningoceles or coexisting structural neurologic pathologies in LMS patients, these prior reports have begun to lay the foundation for optimal neurosurgical management strategies. Brown et al. [34] recommended cerebrospinal fluid diversion via ventriculoperitoneal shunt as the primary treatment of multiple lateral spinal meningoceles. They postulated that endoscopic third ventriculostomy may not be an effective management option as the procedure may alter cerebrospinal fluid flow dynamics to such a degree to cause interval enlargement of the spinal meningoceles. Moreover, they propose patients with LMS and Chiari I malformations undergo the standard neurosurgical in-

tervention for symptomatic Chiari I malformations in addition to ventriculoperitoneal shunt placement as a reduction in supratentorial pressure may translate to a reduction in spinal meningocele pressure [34]. Nevertheless, the long-term effects of cerebrospinal fluid diversion in the context of thoracolumbar spinal meningoceles remain to be elucidated. Several reported cases performed multilevel laminectomies in order to achieve resection of a symptomatic spinal meningocele [25, 27, 29]. However, the majority of individuals with LMS exhibit significant pathologic changes in spine morphology, such as posterior scalloping of the vertebrae, widening of the spinal canal, and/or scoliosis. Indeed, multilevel laminectomies in LMS patients risk destabilizing the spine, which would require an instrumented spinal fusion procedure to maintain spinal integrity [25, 27, 29]. These bony changes may increase the risk of intraoperative cerebrospinal fluid leak as well as instrumentation failure in cases where fusions are performed. As such, multilevel laminectomies in the context of spinal meningocele(s) resection should be utilized with caution in cases of LMS.

The surgical management of multiple spinal meningoceles and coexisting structural neurologic pathologies commonly seen in LMS patients is complex and without standardized guidelines. Surgical intervention to treat spinal meningoceles associated with LMS should only be considered when the patient is exhibiting significant symptomatology or progressive deterioration from meningocele mass effect. Moreover, coexisting structural neurologic pathologies must be considered prior to any operative intervention. As patients with LMS exhibit numerous pathologic changes to spine morphology, we recommend against multilevel laminectomies as this technique risks the structural integrity of the spinal column. Moreover, we recommend against direct manipulation of meningoceles via direct meningocele ligation or meningocele shunting as such techniques are associated with neurologic morbidity and likely only temporary solutions [18, 28, 32]. However, based upon the current literature, we recommend cerebrospinal fluid diversion via placement of a ventriculoperitoneal shunt as a first-line surgical treatment option for patients with symptomatic thoracolumbar meningoceles. The aim of cerebrospinal fluid diversion is to decrease supratentorial pressure, which may translate into a reduction in meningocele wall pressure, and, ultimately, relieve associated symptomatology from meningocele mass effect. Nonetheless, the long-term effects of cerebrospinal fluid diversion on growth rates of multiple thoracolumbar meningoceles remain to be determined.

Screening and Surveillance Recommendations

There are currently no established guidelines for screening or surveillance for LMS. Indeed, LMS is an exceedingly rare diagnosis and, with the exception of medical geneticists, most practitioners are unaware of this clinical syndrome. As such, the medical community may underdiagnose LMS due to the widespread lack of awareness of this clinical entity. Nevertheless, LMS should be considered in children with similar craniofacial dysmorphisms observed in connective tissue diseases who exhibit persistent neurologic symptomatology (e.g., low back pain, hypotonia, sensory deficits). Such complaints should prompt imaging studies of the thoracolumbar spine to rule out the presence of meningoceles. Individuals with craniofacial dysmorphisms and multiple lateral spinal meningoceles warrant evaluation by a medical geneticist and molecular genetic testing for a *NOTCH3* exon 33 mutation. Moreover, Brown et al. [34] recommended screening LMS patients for structural neurologic anomalies found to be associated with this syndrome including Chiari I malformation, syringomyelia, scoliosis, and tethered cord. Close clinical monitoring and radiographic surveillance of these individuals should be implemented to assess for the interval enlargement of the spinal meningoceles or progression of other structural neurologic pathology.

Conclusions

NOTCH3 truncation mutations within exon 33 cause diffuse dysfunction of connective tissue and the unique presence of multiple lateral thoracolumbar spinal meningoceles. Certainly, LMS exhibits novel genetic loci, unique phenotypic appearance, and complex neurosurgical management distinct from other connective tissue

disorders. With each reported case, we gain a better understanding of this exceptional connective tissue disorder and further elucidate optimal neurosurgical management strategies.

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Statement of Ethics

The present manuscript is a literature review. As such, informed consent and institutional board review approval were not necessary to be obtained.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

J.A.C., B.J.K., and C.M.B.: conception of the work. J.A.C., H.L.G., and A.K.: acquisition of the data. J.A.C., E.A.M., and L.S.A.: analysis and interpretation of the data. J.A.C., B.J.K., C.M.B., H.L.G., and A.K.: drafting of the work. J.A.C., E.A.M., and L.S.A.: critically revising the work for intellectual content. J.A.C., B.J.K., C.M.B., H.L.G., A.K., E.A.M., and L.S.A.: approval of the final manuscript. J.A.C., B.J.K., C.M.B., H.L.G., A.K., E.A.M., and L.S.A.: agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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