Occult Spinal Dysraphism

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Preface

Our knowledge of the occult spinal dysraphisms has evolved significantly since the first observations of the various manifestations of this term. Spinal dysraphisms, in general, have been observed and studied by many greats in the history of medicine including Morgagni and von Recklinghausen. The term is attributed to Lichtenstein (1940) who in describing dorsal midline fusion defects found that this constellation of pathological findings was "adequately designated by the term dysraphism or *status dysraphicus*." Interestingly, the occult forms of spinal dysraphism have usually had less attention paid to them compared to their cousins, the open varieties. Surgeons (e.g., James Gardner, C.C. Michael James, and L.P. Lassman), obviously, have also had a keen interest in these embryological derailments and have added to our understanding of their morphology and best surgical treatments, especially in terms of the tethered cord syndrome, which is now, but not historically, an accepted pathological concept. We now know that clinicians should suspect spinal cord tethering in all occult spinal dysraphic states and intervene prior to loss or further loss of neurological function. Parenthetically, James and Lassman, in the early 1970s, rightfully summarized that the spinal dysraphisms:

> became a subject of urgency because its spinal surgical management had a very bad reputation, and because the patients, being children, were developing more severe disabilities without the apparent possibility of treatment of the primary condition.

We now realize that not only children but also undiagnosed adults can present with symptoms of the tethered spinal cord due to an underlying occult spinal dysraphism. Some forms of the occult spinal dysraphisms, such as the isolated fatty infiltrated filum terminale, with minimal caudal displacement or a normally positioned conus medullaris have undergone surgery with questionable to inappropriate indications. Prospective and randomized studies with strong methodologies are necessary in the future to offer guidelines for such cases in order to minimize unindicated surgeries.

In this book, we have endeavored not only to shed light on each of the *forme frustes* of occult spinal dysraphism but also to update the reader to newer embryological insights, modern imaging modalities, and best treatment paradigms. To this end, our hopes are that the clinician, whether they be a specialist or generalist, will

finish reading this text and come away a little wiser and that this knowledge will benefit patient care.

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Historical Perspective of Occult Spinal Dysraphism

1

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Introduction to Spinal Dysraphism

The first known account of spinal dysraphism was published during the seventeenth century. Anatomist Nicolaes Tulp (Fig. 1.1), famously portrayed in Rembrandt's painting "The Anatomy Lesson of Dr. Nicolaes Tulp," described congenital spinal abnormalities in his textbook *Observationes Medicae*. In the 1641 edition, he described six cases of spinal dysraphism and first introduced the term "spina bifida," literally "split spine." One of the cases, involving a lumbosacral lesion, was described as having "the prolongations of the nerves scattered in different directions through the tumor" [1]. In 1691, the Dutch surgeon Frederik Ruysch (Fig. 1.2) published ten case reports of spina bifida. Among other findings, Ruysch was the first to posit that a link existed between spina bifida and hydrocephalus [2]. Ruysch, like Tulp, recommended against surgical intervention because of the high morbidity and mortality, considering the condition inoperable [1]. There have been many subsequent publications on dysraphic states, but there are several disagreements about the pathogenesis and clinical importance of the condition and about

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Fig. 1.1 Nicolaes Tulp

surgical interventions. Reviewing the history of occult spinal dysraphism, we found that no authoritative works were published until the mid-twentieth century, when a steady flow of clinical evidence helped to more clearly delineate the pathologies and abnormalities associated with occult spinal dysraphism. The creation of a methodology for identifying and managing occult spinal dysraphism has helped the medical community offer more effective therapeutic approaches and guidelines.

Early Accounts and Descriptions

The dysraphic state, as described in the book of that name by Gardner (1973), refers to abnormal closure of the neural tube during neonatal development, as opposed to *araphia*, meaning non-closure of the neural tube [3]. Although the terminology associated with spinal dysraphism is of more recent origin, nineteenth century

Fig. 1.2 Frederik Ruysch

French anatomist Jean Cruveilhier (Fig. 1.3) was the first physician to theorize, using anatomical and clinical evidence, that spinal dysraphism was the result of a developmental abnormality [2]. Under the category of spinal dysraphism fall a range of conditions varying in clinical and pathological severity. Regarding the definition and classification of dysraphic states, the first point is that the various macroscopic pathological findings distinguish specific subtypes of dysraphia. The scope of this chapter is *occult* spinal dysraphism (OSD), *occult* referring to that which is hidden. As noted by Tubbs et al. [4], these anomalies are almost entirely restricted to bony elements (vertebrae), and the underlying lesion is completely covered with the skin. This distinguishes OSD from its counterpart, *spina bifida cystica*. The occult dysraphic states include tethered cord syndrome, dilated spinal canal, posterior and anterior spina bifida, and split cord malformations [2]. Although the occult form remains covered with the skin, there can still be various external clues to an underlying pathology. Friedrich Daniel von Recklinghausen, a contemporary of Cruveilhier, was the first anatomist to document the association of lumbosacral hypertrichosis, one of these external clues, with spina bifida occulta [2]. Since then,

Fig. 1.3 Jean Cruveilhier

many other conspicuous anomalies have been clinically linked to occult spinal dysraphisms. Tubbs et al. describe the "enigmatic human tail," noted in India and among peoples of remote islands in the Atlantic Ocean by Pliny and Pausanias, during the first and second centuries, respectively [4]. Although rare, such stories persisted through the centuries – their link to occult spinal dysraphisms still unknown. However, in a 2013 case report, Melo et al. [5] described three cases of human tails, all three of which showed underlying spinal dysraphism as revealed by magnetic resonance imaging. James and Lassman outlined other cutaneous findings such as subcutaneous lipomas, hypertrichosis as mentioned in the case by Virchow, angiomas, and dermal sinus tracts [6]. The growing documentation and understanding of conspicuous abnormalities associated with occult spinal dysraphisms has allowed medical professionals to more quickly render an effective diagnosis for patients with these conditions.

Spinal dysraphism was introduced into the medical lexicon by Friedrich Bremer, a German neurologist, in 1926 [7]. In 1940, Lichtenstein reintroduced the term to denote defective fusion of the neural tube in the dorsal midline during embryo development, which can cause phenotypic abnormalities in the following germ layers: somatic ectoderm (cutaneous), mesoderm, and neuroectoderm [8]. These present with various clinical manifestations involving abnormalities of the skin, muscles, vasculature, and nervous system. Lichtenstein drew attention to many cases that seemed more obscure and sometimes lacked the cutaneous or other external findings frequently seen with overt spina bifida: *occulta*, as it would come to be described. By definition, therefore, spinal dysraphism includes all forms of spina bifida: occulta, aperta, anterior, and posterior [9].

The designation *spina bifida occulta* is credited to Rudolf Virchow (Fig. 1.4). While the external lesions of meningoceles and myelomeningoceles are clearly visible, those of spina bifida occulta are not. In 1875 he addressed the *Berliner Gesellschaft für Anthropologie* regarding a case presented a few months earlier by Dr. Bernhard Ornstein in Athens. Dr. Ornstein had described a Greek soldier "whose loins presented an abundant crop of long hairs. The hairy growth occupied the middle line of the back, and extended thence on each side. The hairs were so long, that the man found it necessary periodically to cut them, in order to prevent interference with defecation" [10]. Virchow, who at the time was working in the

Fig. 1.4 Rudolf Virchow

Institute for Pathology at the Charité teaching hospital in Berlin, noted in his address that he had encountered a similar case of a 24-year-old female who had died from peritonitis secondary to typhoid fever. Virchow described a patch of hair measuring 10 cm in width, the hairs being 6–7 cm in length, with normal-appearing skin at the site. This patch, which he likened to the tuft of feathers on a Polish fowl and therefore called a "tuft of hair," was associated with a palpable depression in the spine [10]. On dissection, Virchow found that the upper sacral vertebrae were "replaced by membrane" [10]. He opined at the time that the patch of hair was "the result of local irritation, due to disturbance during the development of the spinal column" [10].

While Virchow is credited with coining the term, cases had been documented during the seventeenth century (see above). Along with Tulp and Ruysch, Govert Bidloo (Fig. 1.5), an anatomist, playwright and student of Ruysch, published a case in 1708 in his surgical book *Exercitationum Anatomico-Chirurgicarum*, which was probably the first documented lipomyelomeningocele [11]. On autopsy, the conus

Fig. 1.5 Govert Bidloo

medullaris was found within the sacrum. Lipomyelomeningoceles are a form of OSD. According to Bosmia et al. [12], Johnson was credited by Rogers in 1971 with the first description of what was later called "lipomyelomeningocele." However, it was in fact Bidloo, 172 years before Johnson, who described this form of dysraphism.

Soon after Virchow's description, physicians began publishing case reports of spina bifida occulta and its associated clinical findings. Virchow's own pupil, the aforementioned German pathologist Friedrich Daniel von Recklinghausen (Fig. 1.6), reported a case of a 9-year-old girl who had a tuft of hair in the lumbosacral region with a spinal depression and, on autopsy, confirmed the absence of the fifth lumbar spinal process. He described tethering of the cord at S2 by a fatty tumor and found that the fluid in spina bifida was indeed from the subarachnoid space [1]. The patient also suffered from chronic myelitis of the metatarsals in the left foot with an area of anesthesia. von Recklinghausen reported another case of a man with spina bifida occulta and club foot, a neurotic ulcer, and decreased sensation in the

Fig. 1.6 Friedrich von Recklinghausen

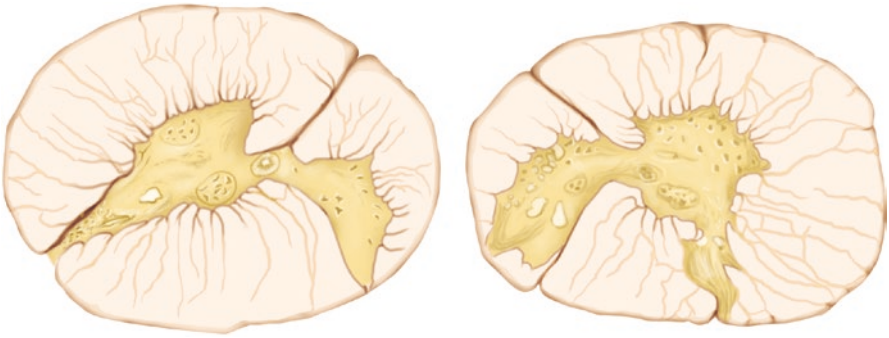

Fig. 1.7 Image of split cord malformation after von Recklinghausen

Fig. 1.8 Conrad Brunner

left foot (Fig. 1.7). Anatomist and physician Johann Conrad Brunner (Fig. 1.8), famous for his research on the pancreas and duodenum and identifying the eponymous "Brunner's glands," had presented a similar case years earlier, which also confirmed that spina bifida occulta is often associated with other physical findings

such as hypertrichosis and club foot [10]. In 1688, he published a case of a newborn with hydrocephalus and a cavity within it, noting a lumbosacral dysraphism and intramedullary cyst that was punctured by another physician, leading to the infant's death. Autopsy showed dysraphia as indicated by failure of fusion of the vertebral arches with myelomeningocele, hydrocephalus, and syringomyelia, described here 150 years before the term was coined. In his conclusion, Brunner believed that the syrinx was either a stand-alone malformation or part of the lumbosacral dysraphia [12].

Giuseppe Muscatello (1866–1951), who had been a pupil of von Recklinghausen at the Institute of Pathology and is credited for his pioneering work in establishing cancer research as its own field and the first cancer center in Italy, also studied spina bifida aperta and occulta. In his various accounts of OSD, he found a dermoid cyst associated with the spinal lesion, other patients with the commonly seen focal tuft of hair, and some with split cords. He even stated his belief that some of these cases were hereditary [13]. These contributions helped establish spina bifida occulta as a clinical entity, sparking wide interest in its pathogenesis and, ultimately, its therapeutic options.

Forms of Occult Spinal Dysraphia

Tethered Cord and Filum Terminale Syndrome

Before Virchow used the term *spina bifida occulta*, a case in 1857, presented by Athol Johnson, a surgeon at the Hospital for Sick Children in Toronto, was probably the first documented instance of tethered cord syndrome, as it came to be known during the latter half of the twentieth century. The patient was a 10-month-old boy who experienced twitches and convulsive movements in the right leg. There was a swelling over the sacrum on which Johnson operated, discovering a lipoma emerging from the spinal canal and adhering to the membranes enveloping the spinal cord. Although documented surgical methods for the treatment of such a condition were at best anecdotal in 1857, Johnson successfully dissected the lipoma from the cord and the patient's twitches completely resolved after the operation [14]. Building upon the work of Johnson, in 1891, W.L. Jones performed what is now called the surgical "untethering" of the spinal cord in a 20-year-old male who had developed incontinence, club foot, and weakness and atrophy of the lower extremities. During his operation, Jones successfully dissected a dense fibrous band, stating that the "spine [was] trephined to relieve pressure on the cauda equine" [15]. The patient was able to walk without pain 6 months after the operation. Johnson and Jones' interventions began providing evidence that occult spinal dysraphisms could potentially be managed with surgery. This represents a break from previous medical opinions regarding the treatment of spinal dysraphism, which tended to advocate for nonintervention due to an extremely high rate of surgical complications. Renowned eighteenth century anatomist Giovanni Morgagni (Fig. 1.9) exemplified this line of thinking when presented with a case of spinal dysraphism in an infant, stating "The life of the little patient, however, is usually cut short by convulsions and other consequences of injury to the nerves; and these evils happen more speedily, if the nerves are pricked in opening the tumour" [2].

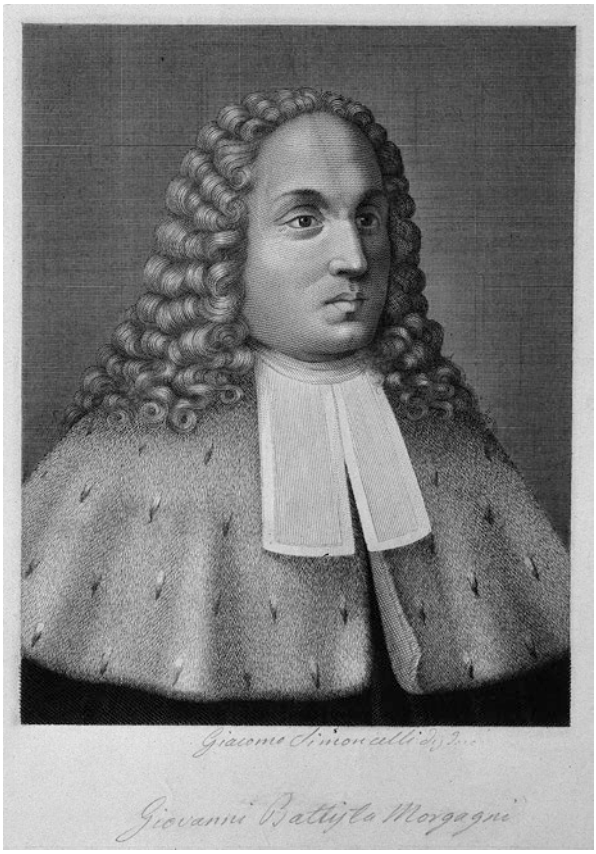

Fig. 1.9 Giovanni Morgagni

Not until 1940 did Lichtenstein first propose that tethering of the cord can cause paraplegia, though his hypothesis was not accepted at the time [16]. In 1953, Garceau (Fig. 1.10), an orthopedic surgeon, whose interest in congenital club foot and scoliosis, among other conditions, led him to discover what he termed *filum terminale syndrome* or *cord-traction syndrome*. Garceau had seen three cases, one with congenital scoliosis, one with idiopathic scoliosis, and one with tuberculosis of the spine, who all experienced lower extremity spastic paralysis. All three underwent laminectomy and resection of a thickened and tightened filum. In the patient with congenital scoliosis, the conus medullaris had remained in its fetal position, and in another patient the filum separated 1 cm after sectioning [17]. On the basis of his surgical findings and postoperative symptom improvement, Garceau posited that tension on the filum, exacerbated by spine flexion, for example, pulls on the hindbrain, displacing it downwards through the foramen magnum, essentially generating a Chiari malformation [15, 18, 19].

In 1976, Hoffman et al. [16] introduced the term *tethered spinal cord syndrome* in a publication on 31 patients who had motor and sensory deficits in the lower extremities. They confirmed that the symptoms improved after dividing a thickened filum terminale. Hoffman, along with Bruce Hendrick and Robin Humphreys, all

Fig. 1.10 George Garceau

three of whom worked at the Hospital for Sick Children in Toronto, advanced the ability of clinicians to recognize and diagnose *tethered spinal cord syndrome* by developing an anatomical definition for the condition. The "3 Hs," as these physicians were collectively known, posited that a radiographic diagnosis of a filum terminale at least 2 mm in diameter and a low-positioned conus medullaris amounted to *tethered spinal cord syndrome* [2, 15, 16]. However, Yamada states that despite these advances, the establishment of *tethered spinal cord syndrome* was fraught with disagreement among physicians and scientists, partly because the evidence for it was based solely on visual findings at surgery [20].

Split Cord Malformation

In addition to tethered spinal cord as a type of OSD, the discovery of split cord malformation (SCM), formerly known as diastematomyelia, further extended the clinical entity. The earliest known case of SCM dates to circa 100 CE in Israel's Negev Desert. The bones of a 20-year-old man were discovered in a tomb and found to have a butterfly vertebra with a bony process dividing the spinal canal into two halves at the thoracolumbar junction [21]. A number of cases were subsequently recorded, describing the same findings as "disjunction" of the cord, per Mathern, Peacock, and Perret in 1624. However, as noted by Saker et al. [21], it was not until 1837 that the pathologist Ollivier d'Angers (Fig. 1.11) coined the term *diastematomyelia*: Greek *diastema*, cleft, and *myelos*, spinal cord. von Recklinghausen, in addition to his aforementioned documentation of spina bifida occulta and associated

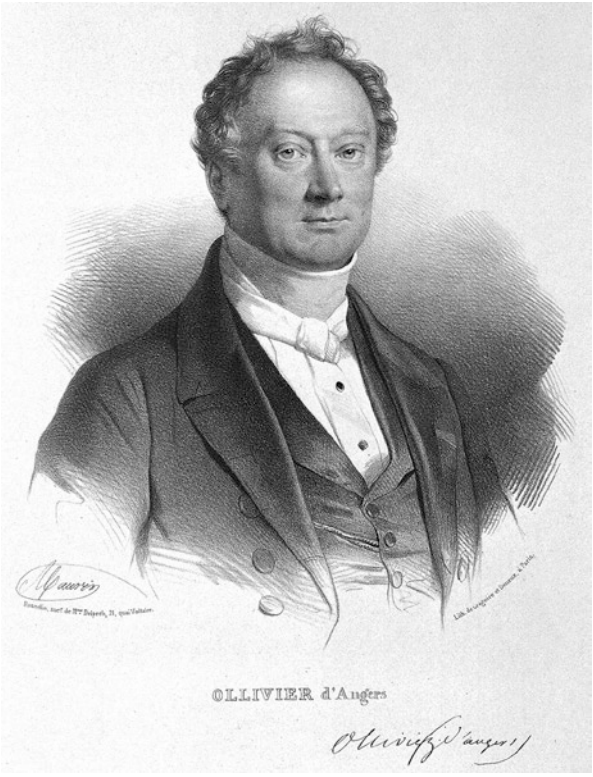

Fig. 1.11 Ollivier d'Angers

clinical findings, remarked on SCM in a 31-year-old female with a split cord from the thoracolumbar spine to the cauda equina. In the ensuing years, Hertwig described the condition as two hemicords within their own dural sacs separated by a bony process – differentiating the finding from what he called *diplomyelia*, wherein the cord itself has been duplicated and there is no such sectioning by a bony process. Herren and Edwards disputed this distinction, stating on the basis of their findings from 42 autopsies that the cord is in fact duplicated [21]. The confusion among terms has persisted, highlighting the need for a more concise and accepted classification system.

In 1886, Humphry published findings from the dissections of six specimens with spina bifida, which account for early descriptions of diastematomyelia. One specimen was described as having deficiencies in the vertebral arches above the spina bifida with a notable projection of bony processes from the vertebral bodies, bisecting the spinal cord. In another specimen, Humphry found a similar presentation in lumbosacral spina bifida with a median process perforating the spinal cord directly above it and severe anatomical abnormality in the vertebral bodies of the lower spine [22]. In 1973, Gardner, whose work on dysraphic states was mentioned earlier, described diastematomyelia as an asymmetrical and longitudinal division of the spinal cord. He noted that at the spinal level involved there is often shortening, scoliosis, or fusion between vertebral bodies, the spinal canal is widened, and the

two hemicords are commonly contained within separate dural sacs and less commonly within the same one [2].

To avoid confusion of terminology and definitions, Pang et al. [23] set out to classify the condition succinctly, using the following three points as criteria for classification: the presence of two cords, the nature of the dural sacs, and the characteristics of the median septum. He distinguished type I and type II SCM, type I having two hemicords each within its own dural sac, separated by a midline bony septum, and type II having two hemicords within a single dural sac, separated by a nonrigid, fibrous median septum [23].

Dysraphia Since the Mid Twentieth Century

These dysraphic states were extensively researched during the 1940s by Ingraham, who documented associated congenital anomalies and provided criteria for surgical intervention. Through the 1950s to the 1970s, James and Lassman, inspired by the works of Ingraham, furthered understanding of OSD states in their authoritative book *Spinal Dysraphism: Spina Bifida Occulta* [9]. Their focus was spina bifida occulta, distinct from overt spina bifida or *aperta*. In a 1972 publication, they noted that spina bifida occulta had been "regarded as a curiosity rather than as an entity with possible clinical implications" as it was often discovered on routine X-rays but not remarked clinically [6].

James and Lassman relied on a distinction they attributed to Koch, whereby macroscopic surgical exploration of the spine revealed no herniation of neural contents [9]. During the preceding years, spinal surgical management had entailed high morbidity and mortality, particularly before the introduction of antibiotics in the 1940s. The authors noted an urgency to survey the literature and begin their own research to improve management and outcomes. James and Lassman suggest the following reasons for this urgency:

> The clinical importance … lies in the extrinsic anomalies which bind down the spinal cord or its nerve roots and prevent them from changing their position within the vertebral canal as they normally should to accommodate the growth of the vertebral column and of the spinal cord. If the spinal cord is tethered it will suffer a traction force during vertebral growth which it can accommodate to some degree in some cases by increasing its rate of growth, but when this compensatory reaction can do no more, the traction force will cause failure of neuronal conduction and ischemia owing to failure of blood supply or to venous congestion with possible thrombosis… It is all these factors which produce the changes in the lower limbs, bladder and bowel. [9]

Their research has since helped to establish recommendations for when surgical intervention is appropriate. It also initiated a thorough analysis of associated clinical findings in patients with spina bifida occulta, intended to help the physician in early diagnosis and consequently to achieve better clinical outcomes [9].

James and Lassman are particularly known for their work on tethered spinal cord syndrome, and in 1972 they published their findings and coined the term *meningocele manqué* (MM). Manqué (French) refers to that which is lacking; the authors posited that the bands are remnants of meningoceles that had failed to mature during embryo

development [24]. Various cases since James and Lassman's publication have challenged the claim that tethering bands terminate at the inner aspect of the dura. Although their definition did not provide a strict guideline for termination locations as a qualification for MM, they modified the definition in 1977, stating that bands can terminate outside the dura in defective laminae of the vertebrae or in the skin [24]. Rajpal et al. [25] also challenged the classification in 2007, setting out to establish a system that classed tethering tracts as "short tethering tracts" and "long tethering tracts," further distinguishing the two on the basis of histological features as having either epithelial or non-epithelial components. This eventually led to placing what would once have been classified under MM into distinct categories, i.e., dermal sinus tracts and limited dorsal myeloschisis. As observed by Schmidt et al. [24] there can be further subdivisions, but the authors note that MM is an entity in itself, adequately defined as "tethering of the spinal cord, nerve roots, and/or filum terminale by single and/or multiple aberrant nerve roots, fibrous bands, and/or adhesions, which terminate onto the dorsal dura mater, epidural space, or overlying lamina" [24].

Lastly, Dr. Shokei Yamada (1926–2017) (Fig. 1.12) who was a Professor and Chairman Emeritus for the Department of Neurosurgery, Loma Linda University School of Medicine, contributed significantly to our current understanding of the tethered cord. He developed an experimental model of tethered spinal cord and was editor for books on this topic [20].

Fig. 1.12 Shokei Yamada

Conclusion

Occult spinal dysraphism has an extensive history with a plethora of cases documented in the medical literature since the seventeenth century, and there are also cases from antiquity that we would class retrospectively as spinal dysraphism. Renowned pathologists such as Virchow and von Recklinghausen began an inquiry into cases of neurological deficits and apparent orthopedic cases such as club foot to initiate better understanding of this clinical entity, which Virchow termed spina bifida occulta. Furthermore, the work of more contemporary surgeons such as Athol Johnson, W.L. Jones, Harold Hoffman, and Shokei Yamada significantly advanced the ability of medical professionals to recognize, classify, and actively manage occult spinal dysraphisms. It is on the shoulders of these and other giants in the field that our current understanding of such neurological derailments is based.

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Embryology of Occult Spinal Dysraphisms

2

Mark S. Dias and Elias B. Rizk

Normal Early Human Neural Development

Blastogenesis, Gastrulation, and Early Notochord Formation

During the first 4 days after fertilization (postovulatory day (POD) 1–4 [1]), the human embryo undergoes about 5 cell divisions to form a mass of approximately 32 cells (the blastocyst) that surrounds a central cavity (the blastocystic cavity). The blastocyst contains an eccentrically located inner cell mass, the embryonic cell proper, and a thinner surrounding ring of cells, the trophoblast (Fig. 2.1). By POD 4, the inner cell mass develops two distinct layers: cells on the dorsal surface, adjacent to the trophoblast, form the *epiblast* while cells on the ventral surface, adjacent to the blastocystic cavity, form the *hypoblast* [1].

By POD 7–12, two additional cavities develop (Fig. 2.1): the *amnionic cavity* appears between the epiblast and the overlying trophoblast cells, while the *umbilical vesicle* (or *yolk sac*) appears below the hypoblast [1]. By POD 13, the hypoblast thickens cranially to form the prochordal plate, the first morphological indication of cranio-caudal orientation. The prochordal plate will give rise to the cephalic mesenchyme and portions of the foregut [1]; maldevelopment of the prochordal plate may be responsible for the malformations associated with holoprosencephaly and agenesis of the corpus callosum [2].

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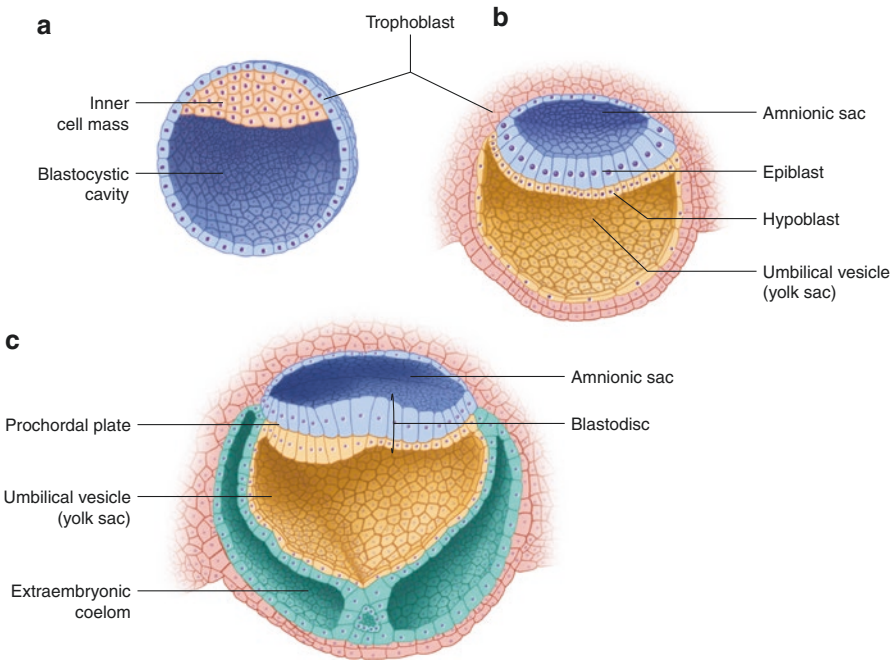


Fig. 2.1 Development of the blastocyst; midsagittal illustrations. (**a**) Continued proliferation of cells produces a sphere containing a blastocystic cavity surrounded by an eccentrically located inner cell mass and a surrounding ring of trophoblast cells. (**b**) The inner cell mass develops further into a two-layered structure, the blastodisc, containing the epiblast adjacent to the amnionic cavity and the hypoblast adjacent to the yolk sac. (**c**) With further development, the blastodisc thickens cranially to form the prochordal plate. (Adapted from Dias and Walker [90])

The primitive streak (PS) first develops at the caudal end of the blastocyst on POD 13 and elongates cranially over the next 3 days (Fig. 2.2a). It reaches its full length by POD 16, occupying the midline in the caudal half of the embryo, and thereafter begins to regress – becoming shorter and migrating back toward the caudal end [1]. The PS ends cranially as *Hensen's node; a* midline *primitive groove* along the length of the PS ends cranially at Hensen's node as the *primitive pit* (Fig. 2.2a).

During both primitive streak elongation and regression, cells of the epiblast migrate toward the primitive streak and invaginate through the primitive groove (Fig. 2.2a). Cell movements during this time are controlled by fibroblast growth factor 8 (FGF8) which, by downregulating the cell adhesion E-cadherin, weakens cell adhesion. FGF8 also controls the expression of *brachyury* (T) and the conversion to a mesodermal fate. The first cells to ingress are prospective endodermal cells which displace the hypoblast cells laterally and replace them to form the definitive endoderm [3–7]. Later, prospective mesodermal cells ingress between the epiblast and the newly formed endoderm to become the mesoderm [6, 7].

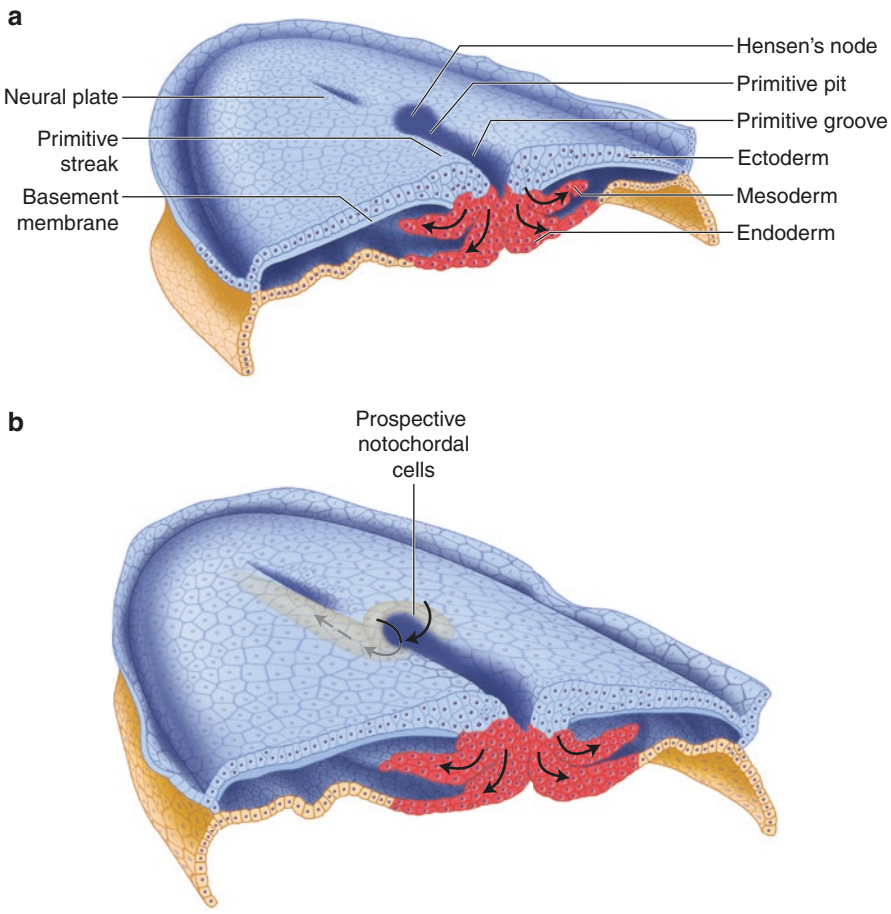


Fig. 2.2 Normal human gastrulation. (**a**) Prospective endodermal and mesodermal cells of the epiblast migrate toward the primitive streak and ingress (arrows) through the primitive groove to become the definitive endoderm and mesoderm. (**b**) Prospective notochordal cells in the cranial margin of Hensen's node will ingress through the primitive pit during primitive streak regression to become the notochordal process. (Adapted from Dias and Walker [90])

Mesodermal derivatives include the midline *notochord* and the more lateral somitic mesoderm; the notochord and somites will both contribute to the formation of the vertebral column. The remaining epiblast cells will form both neuroectoderm and cutaneous ectoderm. This process, called *gastrulation*, transforms the embryo from a two-layered structure containing epiblast and hypoblast to a three-layered structure containing ectoderm, mesoderm, and endoderm [8].

The notochordal process is formed from cells in Hensen's node beginning on POD 16, during PS regression (Fig. 2.2b) [1] and is composed of cells that are radially arranged about a central lumen called the *notochordal canal* [1]. The

notochordal canal is continuous dorsally with the amnionic cavity through the primitive pit [9]. The notochordal process continues to elongate during POD 17–19, reaching its full length on POD 19–21 [1, 10]. During POD 18–20, the notochordal process fuses, or *intercalates*, transiently with the underlying endoderm to form the *notochordal plate* (Fig. 2.3). This process brings the notochordal canal into continuity with the yolk sac, and, since the notochordal canal is already continuous with the amnionic cavity, this creates a direct communication, called the *neurenteric canal*, between the amnion and yolk sac [1]. Between POD 21 and 25, the notochordal plate rolls up and separates once again from the endoderm [1, 11, 12], a process called *excalation* (Fig. 2.3), obliterating the neurenteric canal and once again separating the amnionic and yolk sacs. All but the caudal most notochord is formed in this manner from Hensen's node; the caudal most notochord is derived from the *caudal eminence* or *end bud* at the caudal end of the embryo [11, 13]; the process of secondary notochord formation accompanies *secondary neurulation* and will be described subsequently.

Primary Neurulation

The human neuroectoderm is first visible on POD 16 as a pseudostratified columnar epithelium (Fig. 2.4a), attached peripherally to the surrounding cutaneous ectoderm [14]. By POD 17–19, the *neural groove* develops as a trough immediately above the midline notochord [10]. By POD 19–21, the edges of the neural plate begin to elevate laterally (Fig. 2.4b) [15]. As the neural folds elevate, the adjacent somites begin to form in a rostrocaudal direction [15]. Paired dorsolateral hinge points (DLHP), analogous to the midline neural groove, develop later in the cranial neural tube and the future lumbar spinal cord but *not* in the future cervico-thoracic spinal cord (where closure involves solely elevation of the neural folds about the midline neural groove). The DLHP cause the neural folds to converge toward the midline (Fig. 2.4c). The converging neural folds meet and fuse (Fig. 2.4d) to form a closed neural tube between POD 21 and 23. As the neural tube closes, the cutaneous ectoderm separates (a process called dysjunction) to form intact overlying skin. *Neural crest* cells located near the junction of the neuroectoderm and cutaneous ectoderm migrate away from the closing neural tube between POD 28 and 32 [11, 12] [1, 11–13]; these cells will form the cranial branchial arch structures, the meninx primitiva (which gives rise to the pia-arachnoid), melanocytes, Schwann cells, the adrenal medulla, the autonomic nervous system, and the dorsal root ganglia.

The first part of the neural tube to close is the caudal brainstem or cranial spinal cord [12]. Although previously thought to extend linearly from one initial site like a bidirectional zipper, experimental studies in mammalian embryos suggest the presence of at least three discontinuous waves of closure as neurulation proceeds;

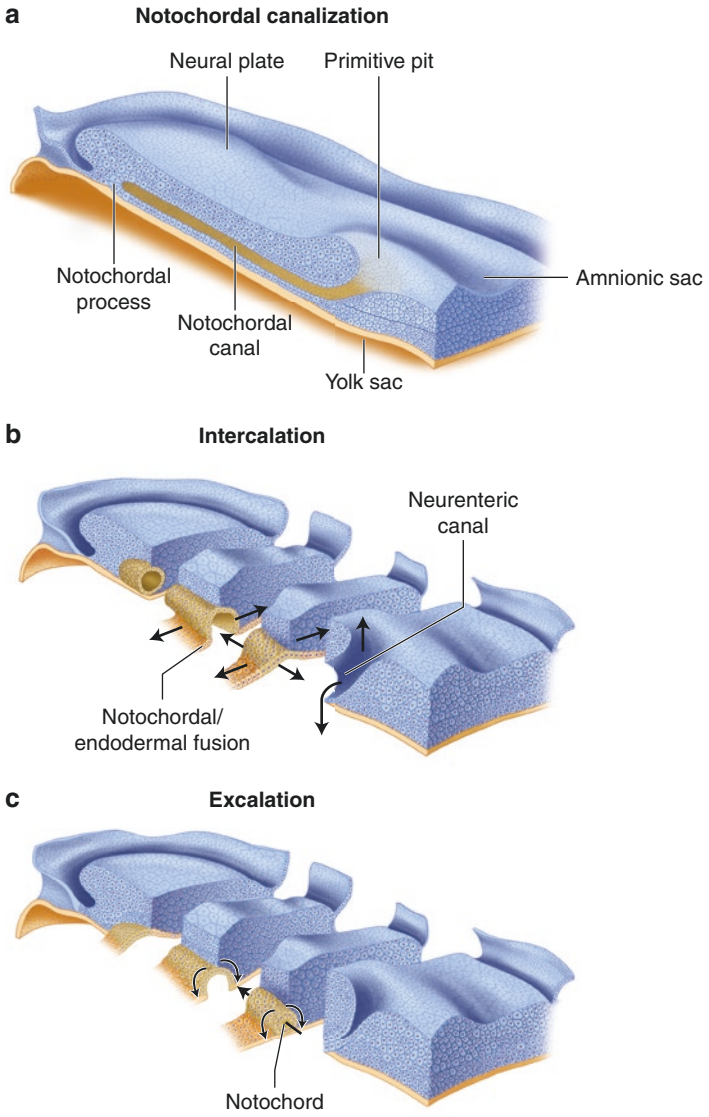


Fig. 2.3 Notochordal canalization, intercalation, and excalation. (**a**) The notochordal process contains a central lumen (the notochordal canal) which is continuous with the amnionic cavity through the primitive pit. (**b**) During intercalation, the canalized notochordal process fuses with the underlying endoderm; the communication of the amnion with the yolk sac forms the *primitive neurenteric canal*. (**c**) During excalation, the notochord rolls up and separates from the endoderm to become the definitive notochord; the primitive neurenteric canal becomes obliterated. (Adapted from Dias and Walker [90])

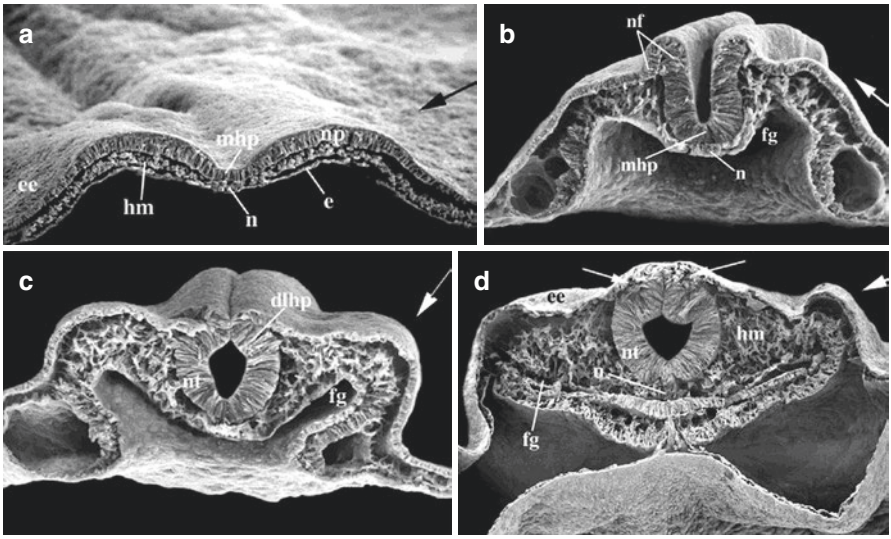


Fig. 2.4 Primary neurulation. (**a**) Flat neural plate stage during shaping and early bending. Furrowing of the neural plate within the median hinge point has occurred. (**b**) Neural groove stage. (**c**) Incipient neural tube stage. The neural folds are in contact with one another but not yet fused. (**d**) Definitive neural tube stage. The neural folds have largely fused forming the roof of the neural tube, neural crest (arrows), and middorsal epidermal ectoderm. *dlhp* dorsolateral hinge point, *e* endoderm, *ee* epidermal ectoderm, *fg* foregut, *hm* head mesoderm, *mhp* median hinge point, *n* notochord, *nf* neural fold, *np* neural plate. (From Colas and Schoenwolf [153]; with permission)

in humans, studies have suggested two such waves [12, 16–18]. Wave I begins bidirectionally from the cervical region. Wave II, which is present in mouse *but apparently not human embryos* [19], begins at the junction of the mesencephalon and prosencephalon and also proceeds bidirectionally to meet Wave I in the occipitoparietal region. Wave III begins in the cranial most neural tube and extends caudally to meet Wave II at the commissural plate, the site of the traditional *anterior neuropore* and the location of the future lamina terminalis [1, 20]. Wave I extends caudally from its origin to the *caudal neuropore* at the second sacral segment of the neural tube [17, 18]; secondary neurulation forms more caudal neural tube (tip of the conus and filum terminale). Accordingly, one can deduce that *all spinal malformations which arise cranial to S2, whether open or closed, involve regions of the neural tube which are formed from primary neurulation*. The distribution of neural tube defects largely parallels the sites of the neuropores (lamina terminalis and lumbosacral spine) [16, 21].

From a cellular and molecular standpoint, primary neurulation is comprised of three distinct but temporally overlapping events: (1) specification and remodeling of the neuroepithelium during embryonic "convergent extension"; (2) neural plate bending accompanied by elevation and convergence of the neural folds; and (3) neural fold fusion.

Convergent extension (CE) involves rostrocaudal elongation and mediolateral convergence of embryonic tissues (including notochord, mesodermal, and neural

tissues). CE results in a neuroepithelium having a more elongated shape with a bulbous portion cranial to the primitive streak and a thinner, tapering end that abuts the primitive streak as it recedes. CE in both amphibian, avian, and mammalian embryos involves rearrangement and intercalation of neuroepithelial cells [22]; in avian embryos, cell division and cell shape changes likely play an additional role [23]. From a molecular standpoint, CE involves the canonical Wnt/PCP pathway, containing six core proteins that have been highly conserved from *Drosophila* to mammals and encode polarization of cells within the plane of a tissue [24]. The Wnt/PCP pathway acts on intercellular junctions specifically at the anterior-posterior borders, the result of which is phosphorylation of myosin light chain (MLC). This pathway is also involved in subsequent neural plate bending [24]. Mouse embryos containing Wnt/PCP pathway mutations fail to undergo CE and are therefore shorter and wider, having neural folds that are too far apart to adequately converge and fuse. Similar PCP mutations have also been identified in humans with NTDs [24].

During neural plate bending, neuroepithelial cells that overlie the notochord undergo a conformational change in cell shape from columnar to trapezoidal, forming the *neural groove*, *floor plate*, *notoplate,* or *median hinge point* – the first visible sign of neural plate bending to form the neural tube (Fig. 2.5). This "floor plate reaction" is the result of inductive interactions between the notochord and the floor plate cells that involves the sonic hedgehog (*Shh*) pathway (reviewed in [25]). *Shh* induces the overlying floor plate cells to enter the S-phase of mitosis, thereby translocating the nucleus to, and expanding, the basal region of these cells; contraction of apical microfilaments simultaneously constricts the apical region. The net effect is the production of wedge-shaped floor plate cells. Embryos in which the notochord is missing develop a neural tube but lack a floor plate; conversely, transplanting a second notochord to the lateral regions of the neural tube of a host embryo induces an accessory floor plate [26, 27]. In the mouse, loss of *Shh* expression in the head mesenchyme and rostral neural tube results in holoprosencephaly [28].

Elevation and convergence of the neural folds are achieved under both neural and extraneural influences (including changes in the adjacent cutaneous ectoderm and underlying mesoderm), although the relative contributions of each are unclear at present. As the neural folds elevate around the floor plate, a similar cell shape change occurs among neuroepithelial cells at the paired DLHP (Fig. 2.5). The formation of DLHPs is responsible for the medial convergence of the neural folds and is influenced by competitive interactions between notochordally derived *Shh* and so-called "dorsalizing factors" bone morphogenetic protein-2 (BMP-2) and *noggin* expressed by the cutaneous ectoderm. BMP-2 inhibits the formation of the DLHP; the expression of BMP-2 is opposed by *noggin,* the expression of which is inhibited by *Shh*. When *Shh* is ascendant (as it is in the cervical and thoracic regions of the spinal cord), the expression of *noggin* is reduced, the action of BMP-2 is unopposed, and DLHP are absent. When *Shh* is weak (as it is in caudal regions of the spinal cord), *noggin* is expressed, the action of BMP-2 is opposed, and DLHP are present [24]. Successful DLHP formation is likely more important than the floor plate reaction in successfully completing neurulation in the cranium and lumbar

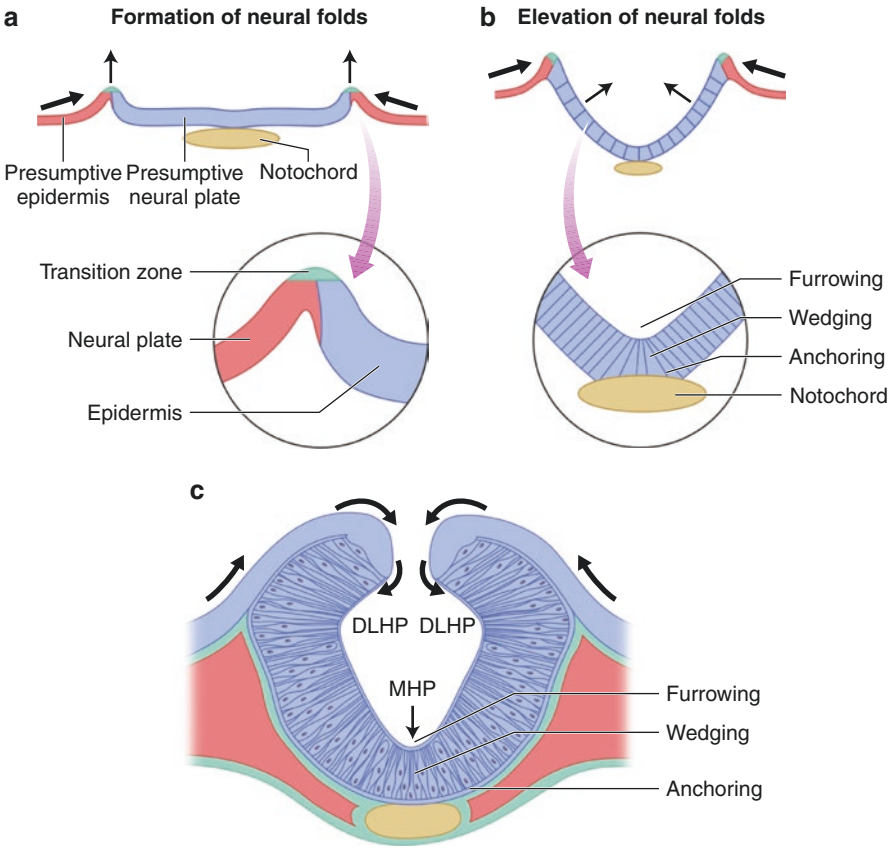


Fig. 2.5 Schematic representation of epithelial bending in avian embryos. (**a**) Formation of definitive neural folds (**b**) Elevation of the neural folds is facilitated by the formation of a median hinge point, but extrinsic forces from the adjacent cutaneous ectoderm (purple arrows) drive the process. (**c**) Convergence of the neural folds. Formation of dorsolateral hinge points (DLHP), structurally and functionally analogous to the median hinge point (MHP), provide a point around which the neural folds bend toward the midline for final apposition and fusion. (Adapted from Moury and Schoenwolf [154])

neural tube; embryos experimentally lacking a notochord (and therefore *Shh*) nonetheless successfully form DLHP and complete neurulation despite an absent floor plate [24]. *Zic-2*, a member of the zinc-finger family, is also involved in DLHP formation. *Zic-2* mutants lack DLHP and have NTDs [24]. Additionally, members of the *Grainy head*-like family of transcription factors play an additional role in the formation of DLHP and completion of Waves II and III and the lumbar neural tube (but not of Wave I, where DLHP are neither present nor necessary for normal neural tube closure); the actions of these transcription factors appear to occur independent of BMP-2, *noggin*, and *Zic-2* [29].

The final event in primary neurulation is the fusion of the converging neural folds, a process that likely involves interdigitations of cell membrane filopodia and

lamellipodia, cell surface glycoproteins, and intercellular junctions of various types. Filopodia and lamellipodia are cell membrane extensions expressed by neural and/or cutaneous ectoderm at the tips of the converging neural folds. Their cell of origin is disputed – in some species they appear to arise from cutaneous ectoderm and in others from neuroectoderm. Their origin, and the cell making initial contact, may also vary according to the level of the neuraxis, with contacts made by cutaneous ectoderm at some levels and neuroectoderm at others [24]. Elimination of Rac1, a protein required for the formation of cellular protrusions, in nonneural cells produces NTDs, whereas elimination from neural cells does not [24]. The role of extracellular matrix and cell adhesion molecules, including laminin, fibronectin, and proteoglycans (principally heparan and chondroitin sulfate), has been extensively studied although their role in neurulation and human NTDs is still incompletely understood.

A number of observations suggest an important role for the homeobox gene *Pax3* in convergent extension and neural fold fusion (reviewed in George and McLone [30]. The geographic and temporal expression of *Pax3* in the dorsal neural tube precisely at the time of neural tube closure suggests that the *Pax3* gene product might be important in neural fold fusion. Antisense oligonucleotides that block the function of *Pax3* result in neural tube defects in mice. Moreover, the locus for the *Splotch* (*Sp*) mouse mutant, which exhibits neural tube defects (exencephaly and myelomeningocele), maps precisely to the *Pax3* locus. Finally, the *Sp* mutant is the mouse homologue of the human Waardenburg syndrome Type I, *Pax3* mutations have been reported in a family with NTDs [31], and a more recent study has demonstrated an association between *Pax3* mutations and human NTDs [32].

A recent study in mice has demonstrated the importance of the Wnt/β-catenin PCP pathway in primary and secondary neurulation that is mediated at least in part by downstream regulation of the *Pax3* gene [33]. B-Catenin knockout mice fail to express β-catenin and *Pax3* in the dorsal neural folds during primary neurulation, particularly at the caudal neuropore, and exhibit NTDs; β-catenin receptors on the dorsal neural tube have been identified, and β-catenin upregulates the transcription of *Pax3* [33]. Interestingly, *Pax3* also reciprocally influences the Wnt/PCP pathway suggesting a complicated and as yet poorly understood relationship.

Secondary Neurulation

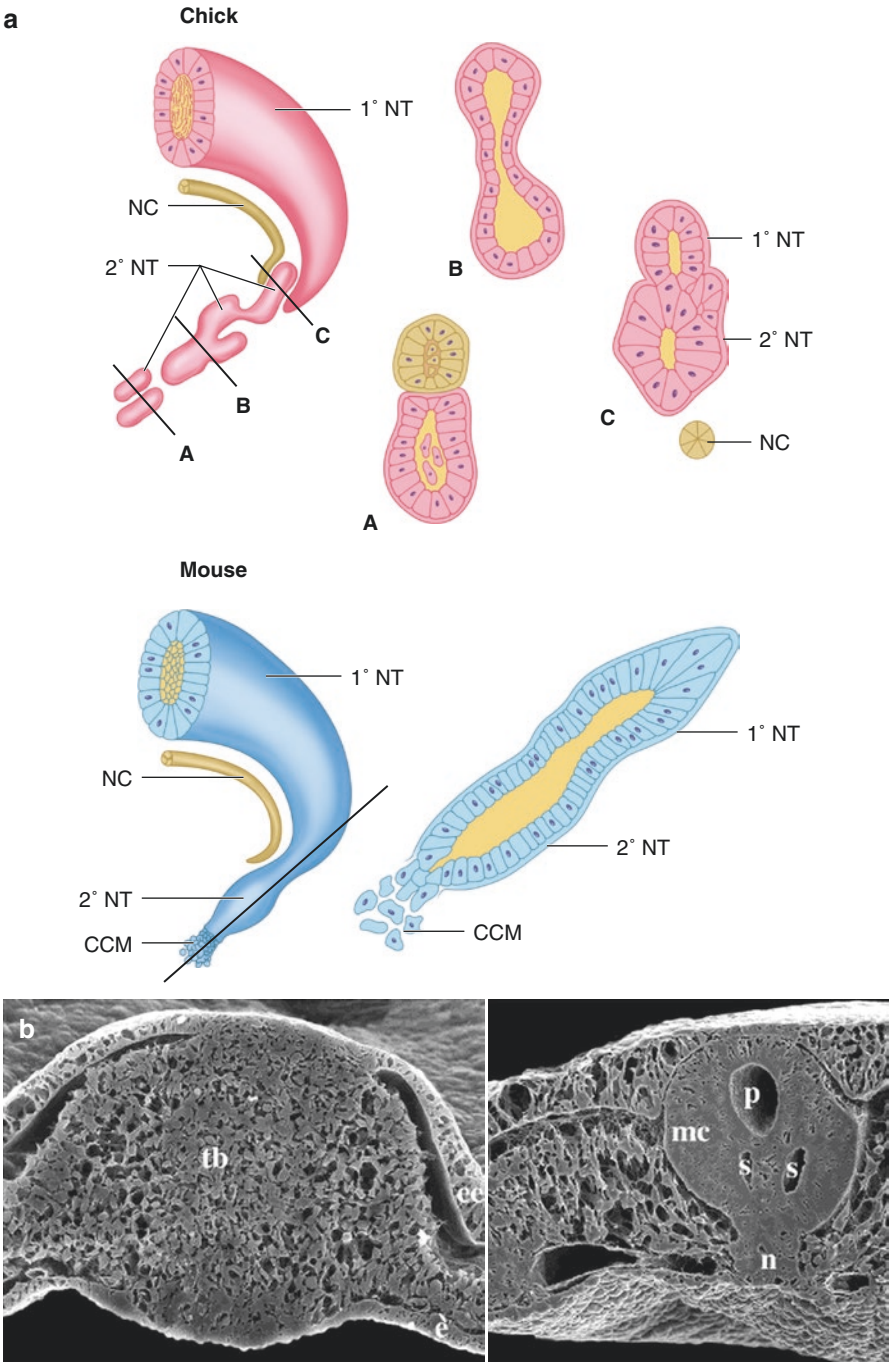
After the caudal neuropore closes on POD 25–27, the development of more caudal neural structures – the terminal conus and filum terminale – takes place through *secondary neurulation* [13]. The primitive streak at this point is referred to as the *caudal cell mass* (CCM) and extends from the posterior neuropore to the cloacal membrane. The cells of the CCM give rise to the neural tube and vertebrae caudal to S2, but not the hindgut or tailgut which are instead derived from endoderm, nor the posterior notochord which is derived from a prospective notochordal region located immediately anterior to the CCM and underlying the primary neural tube [34].

The mechanism of secondary neurulation is different from that of neurulation and is species specific (Fig. 2.6). In avian embryos, secondary neurulation results in the formation of a *medullary cord* (the equivalent of the neural cord in the human) from the dorsal cells of the CCM. Within the medullary cord, an outer layer of tightly packed cells surrounds an inner cluster of more loosely arranged cells. Cavitation between the two cell groups creates multiple tubules with the outer cells surrounding a central lumen, within which are the inner cells. The inner cells are eventually lost, perhaps by incorporation with the outer cell group, cell death, or migration away from the medullary cord, leaving tubules of outer cells surrounding empty luminae. These smaller tubules coalesce to form a single *secondary neural tube* (Fig. 2.6) later fuse with the neural tube formed from primary neurulation [35]. The boundary between the neural tubes formed by primary and secondary neurulation is called the overlap zone, within which the primary neural tube is dorsal and the secondary neural tube ventral.

Mammalian secondary neurulation begins with the formation of a *medullary rosette*, a cluster of CCM cells radially arranged about a central lumen. The cells of the medullary rosette are thought to be the homologue of the outer cell group in the chick embryo; the inner cell group seen in the chick is not present in mammals. Caudal growth of the secondary neural tube occurs by additional cavitation of the medullary rosette and recruitment of additional cells from the CCM [36].

Avian and mammalian secondary neurulation therefore differ in at least two respects. First, the secondary neural tube in mammals is always directly continuous with the primary neural tube and develops caudally from the posterior neuropore, whereas the avian secondary neural tube develops independently and only later fuses with the primary neural tube. Second, the lumen of the mammalian

Fig. 2.6 Secondary neurulation. (**a**) *Upper illustration* depicts secondary neurulation in avian embryos. The medullary cord consists of multiple luminae, each surrounded by an outer layer of tightly packed, radially oriented cells and containing an inner group of more loosely packed cells. Adjacent cords coalesce to form larger aggregates; simultaneously, the inner cells are lost. Eventually a single structure is formed, having a single lumen which is *not* yet in direct communication with the lumen formed by primary neurulation. Later, the neural tube formed by secondary neurulation (2° NT) fuses with that formed from primary neurulation (1° NT); at this point, the luminae of the two neural tubes communicate directly. *NC* notochord. *Lower illustration* depicts secondary neurulation in mouse embryos. A medullary rosette is composed of cells radially arranged about an empty central lumen. The lumen is always in communication with the central canal formed by primary neurulation. Growth of the secondary neural tube occurs by additional cavitation of the secondary lumen and by recruiting additional cells from the caudal cell mass (CCM). (Adapted from Dias and McLone [155]). (**b**) Scanning electron micrographs of secondary neurulation in the chick embryo. The *left image* is at a late gastrulation stage and shows the tail bud (tb) – the equivalent of the caudal cell mass – located between the overlying caudal cutaneous (epidermal) ectoderm (ee) and the underlying endoderm (e). The *right image* is obtained during secondary neurulation and shows the neural tube derived from primary neurulation (p) lying dorsal to the neural tube derived from secondary neurulation (medullary cord, mc), the latter containing two separate cavities (s) that have not yet merged. *n* notochord. (From Moury and Schoenwolf [154]; with permission)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secondary neural tube is single and always in continuity with the lumen of the primary neural tube, whereas the avian embryo initially contains multiple luminae that only later communicate with the lumen of the primary neural tube.

Whether *human* secondary neurulation follows mammalian or avian, morphogenesis has been debated [13, 37, 38]. A more recent study of caudal neural tube formation in 21 human embryos identified multiple caudal neuroepithelial luminae separated from the notochord by intervening mesenchymal tissue; the morphological characteristics and expression of neuronal antigens in this study [39] suggest that human secondary neurulation more closely resembles the chick [40, 41].

The cellular and molecular events underlying secondary neurulation have received increasing attention in animal models. Two distinct proposals have been put forth. One considers the CCM as a blastema capable of generating cells of various types from multipotent precursors; the alternative is that caudal structures are formed through an extension of gastrulation [42]. Beck has suggested that if the CCM functions as a blastema, then there should be a higher rate of proliferation among these cells and have the ability to regenerate; however, studies in amphibian embryos have convincingly demonstrated that it does not have either characteristic [42].

During secondary neurulation in the chick, cells of the medullary cord express both N-CAM and synaptophysin typical of neuroepithelial cells; N-CAM plays a critical role in cellular adhesion during neural tube formation, and both N-CAM and synaptophysin are thought to influence the differentiation of structures derived from the CCM [41]. However, N-CAM is lacking, and synaptophysin only weakly positive, in *human* caudal neural tube and CCM during secondary neurulation [39].

The Wnt/β-catenin pathway has also been implicated in the development of the CCM and therefore of secondary neurulation. Three mammalian homologues of the drosophila gene *Caudal*, called Cdx1, Cdx2, and Cdx4, have been shown to influence the formation of the caudal neuraxis and other caudal structures. All three genes are expressed during the primitive streak and subsequently the CCM, as well as the hindgut endoderm, during gastrulation, and are involved in anterior-posterior embryonic patterning and posterior embryonic elongation. Both the expression and precise timing of *Cdx* influence the development of the posterior neuroepithelium and cloacal derivatives in mouse embryos [43]; compound *Cdx* mouse mutants fail to form caudal tissues derived from the CCM (reviewed in [43]), and *Cdx* is likely involved in both human caudal agenesis and cloacal development disorders. *Cdx2* expression in mice is in turn regulated by the Wnt/β-catenin PCP pathway; *Pax3* is also required but is insufficient to activate *Cdx2* [33]. Mutations in *Shh* and its downstream effectors *Wnt5a* and *BMP4*, as well as retinoic acid and the premature expression of *Hox 13*, have also been implicated in caudal agenesis and cloacal abnormalities (reviewed in [43]). Finally, the brachyury (T) gene is important for caudal, including midline axial and cloacal, development; the T allele is also regulated by the Wnt canonical pathway, suggesting a central role of the Wnt/β-catenin canonical pathway in regulating overall caudal development through all of these downstream mechanisms [43].

Junctional Neurulation

More recent studies in chick embryos have described a separate "junctional neurulation" process, morphologically and molecularly distinct from primary and secondary neurulation, which serves as a transition zone to enjoin primary and secondary neurulation. Fate mapping studies have identified this junctional segment of the avian embryonic neural tube, beginning in the upper thoracic region (corresponding to the thoracolumbar region in humans) and extending caudally, within which neurulation is neither primary nor secondary. Fate mapping studies identify this as a unique region of the neuroepithelium, called the *node-streak border* (NSB) [44] that flanks the primitive streak caudal to Hensen's node as the streak and node regress caudally. The NSB contains two discreet cell populations, each of which express distinct cell markers and undergo unique cell movements (Fig. 2.7). The first group is located more laterally and, like the cells of the neural tube derived from primary neurulation with which it is in continuity, expresses the neural marker *Sox-2* and is underlain by a basement membrane. During neurulation, this group migrates laterally and dorsally in concert with the more cranial neuroepithelium to form neural folds. The second group is situated more medially and is in continuity with the regressing primitive streak. This group initially lacks both *Sox-2* expression and lacks an underlying basement membrane and expresses *Snail-2*, BMP-4, and N-cadherin, similar to those expressed on the adjacent *mesodermal* progenitors within the primitive streak and consistent with an *epithelial to mesenchymal transition* (EMT). Cells in this group migrate caudally along the midline along with Hensen's node and the primitive streak while simultaneously ingressing ventrally. They only later express *Sox-2* and intercalate with the dorsal neuroepithelial cells to form the ventral neural tube in the junctional region (Fig. 2.7). Importantly, these cells are *also* the source of the caudal neural tube generated by secondary neurulation. As such, the junctional region of the neural tube represents a *cranio-caudal transition zone that links primary and secondary neurulation*. Interestingly, this junctional neurulation in chicks occurs largely *before* the neuroepithelium is underlain by a notochord [44].

A member of the Wnt polar cell polarity (PCP) pathway, called *Prickle-1*, which regulates polarized deposition of fibronectin on cell surfaces during convergent extension, is critical to this transition at the NSB. *Prickle-1* is expressed in the NSB but is absent in the neural tube formed from primary neurulation. Moreover, application of *Prickle-1* small interfering RNA (siRNA), which interfere with *Prickle-1* function, during the formation of the NSB reliably produces embryos with mid-level NTDs. Treatment at slightly later times produced more caudal and localized NTDs. Importantly, treatment *during primary neurulation* does not produce NTDs [44].

Eibach and colleagues recently described the human homologue of junctional neural tube defects in three patients in which the upper spinal cord ended bluntly and was attached to an independent lower "conus" with a filum terminale by a thin band of tissue. In one patient, intraoperative electrical stimulation of the upper spinal cord produced lower extremity motor movements down to the L5 level and

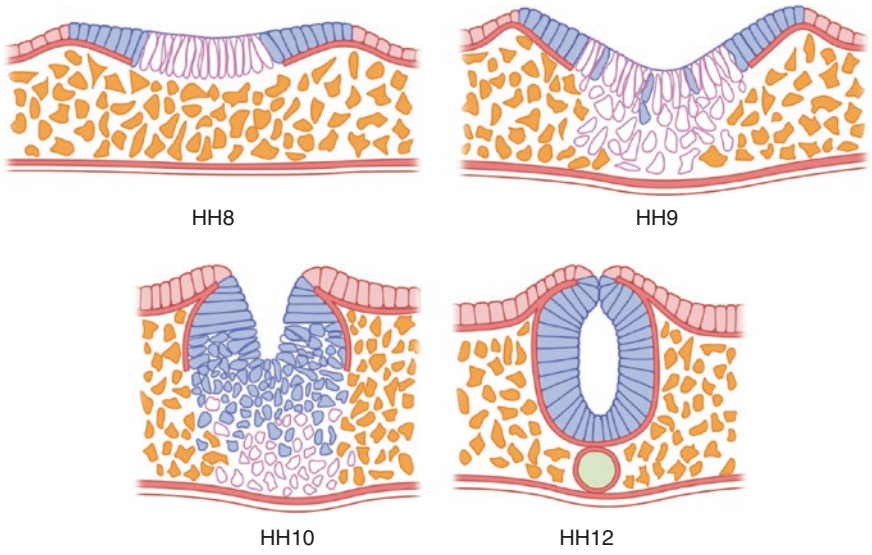

Fig. 2.7 Junctional neurulation. Illustration showing cross sections through the Node Streak Border from chick embryos at the time of junctional neurulation (Hamilton and Hamburger (HH) stages H8-HH12). Purple represents Sox-2-positive neural cells; white represents Sox-2-negative neural progenitors; pink represents ectoderm; green represents notochord; orange represents paraxial mesoderm; thick lines indicate basement membranes. At HH8, the superficial layer of the NSB is constituted of two adjacent cell populations: One is situated laterally and contains Sox-2-positive cells that express E-cadherin and are limited by a basement membrane. The other population, located medially, contains Sox-2-negative cells that are not limited by a basement membrane. During junctional neurulation (HH9 to HH12), the lateral cells undergo dorsal elevation and folding to become neural folds as during primary neurulation, while the medial cells lose their epithelial nature, ingress ventrally, and form a mass of compact cells. These cells later express Sox-2 and reorganize as an epithelium, in continuity with the dorsal neural tube and underlain by a dorsoventral basement membrane. (Adapted from Dady [44])

somatosensory evoked responses (SSEP) from both legs, whereas stimulation of the lower conus elicited motor responses only from the anal sphincter and SSEP responses only from the sensory domain of the pudendal nerve, suggesting that the two regions were both anatomically and functionally separate. The authors proposed that the tissue band separating the two functional spinal cord segments formed by failed junctional neurulation [45].

Ascent of the Conus Medullaris

Beginning on POD 43 and continuing into later fetal development, the neural tube appears to grow slower than the surrounding bony spine, with the conus medullaris ending opposite successively more cranial bony levels as fetal development progresses – referred to as the "ascent of the conus medullaris" (Fig. 2.8a–e) [46, 47]. The ascent involves two mechanisms. Before POD 54, the

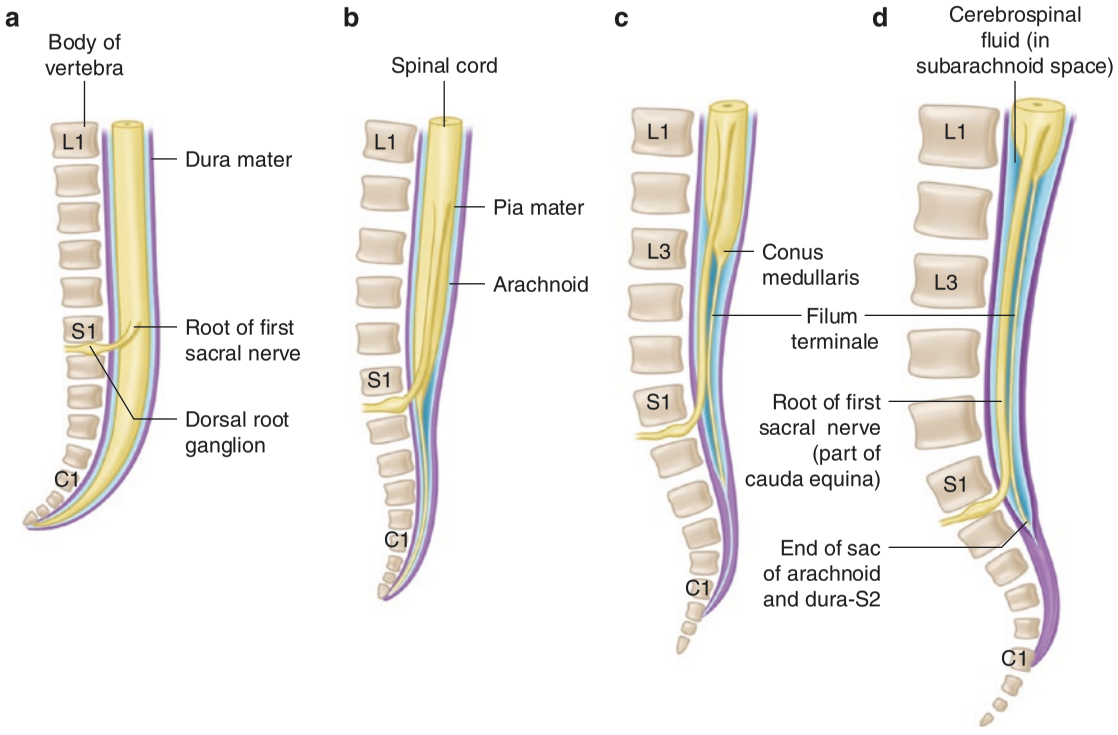

Fig. 2.8 Ascent of the conus medullaris. (**a**–**d**) Show progressive ascent of the conus medullaris during embryogenesis and the immediate postnatal period. (**a**) 8 weeks gestation, (**b**) 24 weeks gestation, (**c**) newborn (**d**) adulthood. ((**a**–**d**) Adapted from Moore [156]). (**e**) Vertebral level of termination of the conus medullaris during fetal and early postnatal life. ((**e**) Adapted from Barson [51])

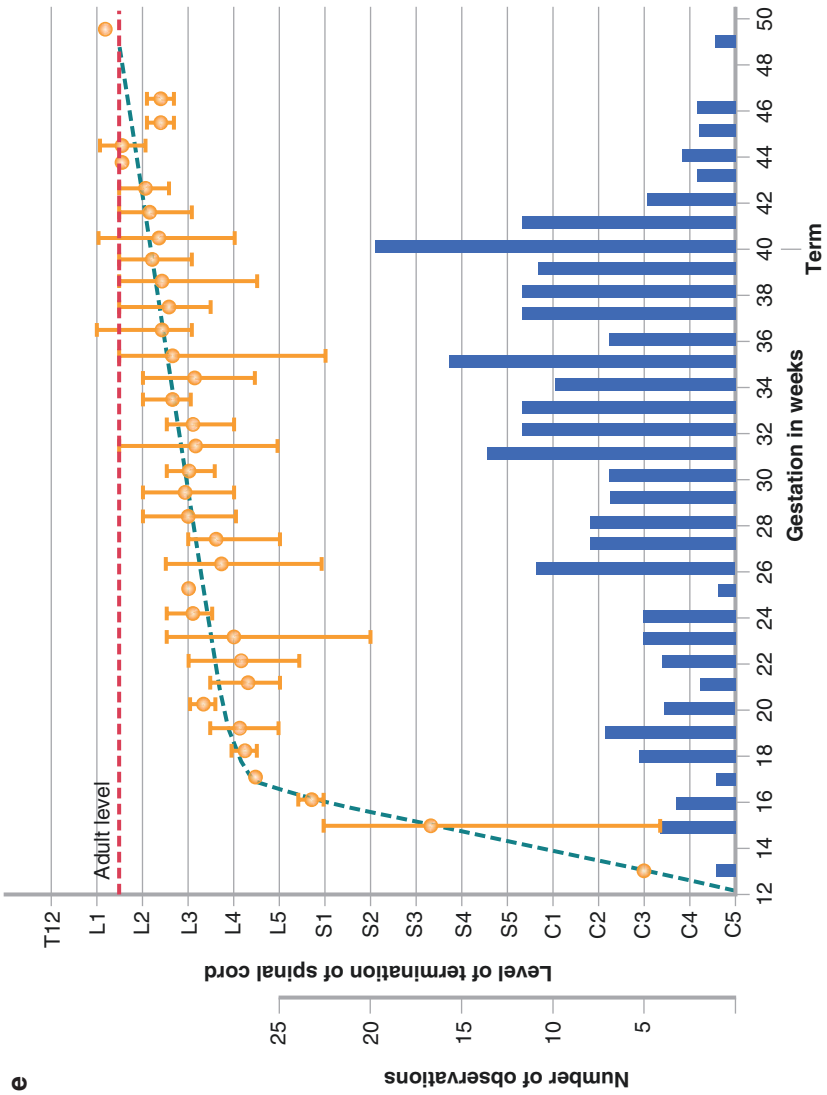

Fig. 2.8 (continued)

caudal neural tube undergoes *retrogressive differentiation* in which the caudal neural tube loses much of its diameter, fails to develop a distinct mantle zone, exhibits only a thin, rudimentary marginal zone, and "generally appears less well developed" than it did at earlier embryonic stages [46]. This involution appears to involve apoptosis [39, 40]. Beyond POD 54, ascent takes place through faster linear growth of the bony spine relative to the neural tube [46, 47].

The rate at which the conus medullaris ascends has been examined by several investigators [48–52]. Most of the ascent occurs between 8 and 25 weeks gestation, slowing significantly thereafter (Fig. 2.8e) [51]. Although earlier studies by Barson suggested that additional ascent was possible through the first two postnatal months [51, 53], other studies suggest the conus achieves an "adult" level at birth [48–50]. All studies confirm that the conus achieves its final level by two postnatal months. A study of the normal conus in children with brain tumors undergoing whole spine imaging confirmed that (1) the conus, on average, ends at the inferior third of the L1 vertebral body, (2) the most common terminus (mode) is the L1–2 disc space, and (3) the lower limit of normal (using a 95% confidence interval) is the *middle-third of L2* [54]. A conus that ends more caudally is therefore considered radiographically "tethered."

Embryogenesis of Dysraphic Malformations

Disorders of early neural development can give rise to a number of human malformations, collectively referred to as *neural tube defects* (NTD) or *dysraphic malformations*. This chapter focuses on the reputed embryogenesis of dysraphic malformations *other than* myelomeningocele and anencephaly, which have been well described elsewhere [19, 22, 55].

Incomplete Dysjunction: Limited Dorsal Myeloschisis, Fibroneural Stalks, and Dermal Sinus Tracts

A number of occult dysraphic malformations incorporate stalks of tissue that extend from an overlying dysplastic skin lesion; penetrate the lumbodorsal fascia, dorsal vertebral elements, and dura; and extend cranially to end on the dorsum of the spinal cord, which contain varying tissue types. The more well known, but *least common*, are pure dermal sinus tracts wherein the tract contains cutaneous ectodermal elements including skin cells, dermal appendages (sebaceous glands, hair follicles, etc.), and dermoid or epidermoid cysts [45, 56]. *More commonly*, however, are tracts that contain peripheral (dorsal roots, dorsal root ganglia) and central (glioneuronal rests) neuroepithelium; mesodermal tissues such as mesenchymal bands, striated muscle, fat, and/or blood vessels; and rarely even endodermally derived neurenteric cysts [57, 58]. These other types have been referred to variably as "dermal sinus-like tracts" [58] or "limited dorsal myeloschisis" [57, 59]. Associated cutaneous anomalies include skin dimples, dysplastic or scarified skin

patches or skin tags, saccular collections of CSF, aberrant hairs, cutaneous appendages or skin tags, and capillary malformations (infantile hemangioma, port wine stain, or salmon patch/flammeus nevus) [60].

These tracts may involve any level of the spinal neuraxis although there is a distinct predilection for the caudal neuropore (caudal end of Wave I; sacral). Lumbosacral tracts arise in the dorsal midline *cranial to the intergluteal cleft* (Fig. 2.9a). The tract penetrates the lumbodorsal fascia and spinal canal (usually within the interspinous ligament or between bifid lamina) and enters the dura immediately beneath (Fig. 2.9b, c); from this point it typically extends cephalad to the conus medullaris, ending at the dorsal surface of the spinal cord cranial to the tip of the conus; a *separate filum terminale* is universally present (Fig. 2.9d). This anatomical arrangement confirms the embryology of these stalks as disorders of primary neurulation since the tract (arising from the dorsum of the spinal cord anterior to the conus) and the filum terminale (derived from secondary neurulation) are separate.

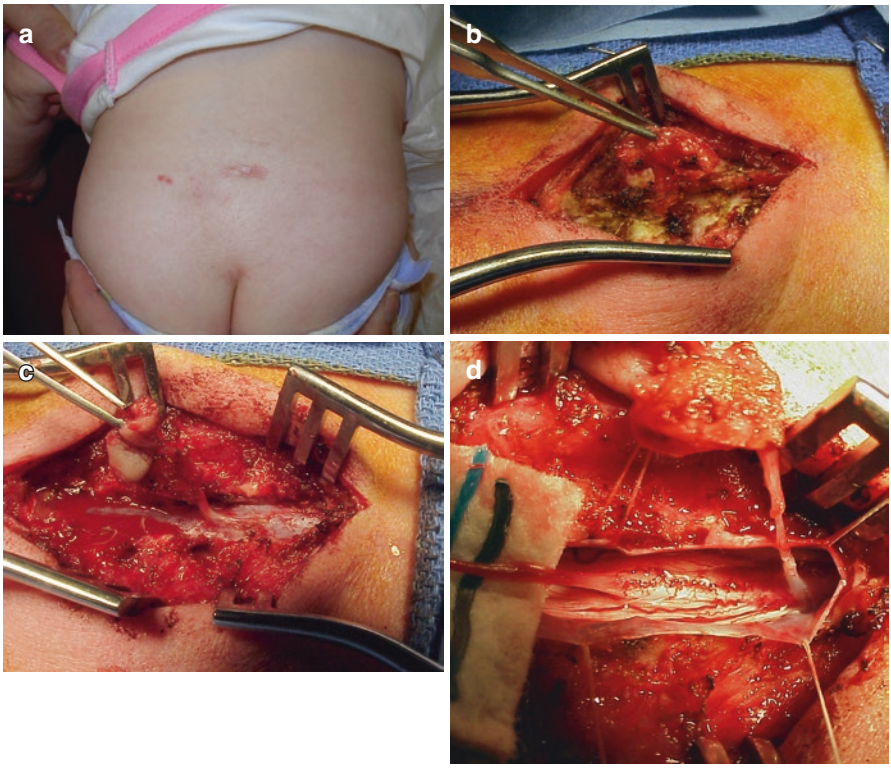

Fig. 2.9 Lumbosacral tracts. (**a**) Infant with a scarified patch on the back, with surrounding capillary hemangioma. (**b**) Lumbar tract in another infant extending through the lumbodorsal fascia and the interspinous ligament between two spinous processes. (**c**) Same tract extending through dura at level of the cutaneous lesion. (**d**) Same tract ending at the midline dorsum of the conus medullaris. Note the separate filum terminale lying on cottonoid patty

It is important to distinguish sacrococcygeal sinuses from the innocent coccygeal dimple, as the latter, which are present in 4% of the normal population [61], are not associated with underlying dysraphic malformations. Coccygeal dimples are simple blind tracts, located more caudally within the intergluteal cleft and overlying the coccyx, extending to the tip of the coccyx, having no associated cutaneous abnormalities, and not associated with tethering lesions; isolated coccygeal dimples are of no clinical consequence [60, 61]. In contrast, pathological sinus tracts are usually more complex, exhibiting cutaneous malformations with uneven margins and associated scarified or improperly formed skin, dimples, capillary malformations, tufts of hair, and/or abnormal intergluteal clefts. Most importantly, pathological tracts lie *cranial to the intergluteal cleft*.

The earliest theory regarding the embryogenesis of these tracts proposed that they arise through faulty separation (dysjunction) of neuroectoderm from cutaneous ectoderm during primary neurulation (Fig. 2.10) [62]. This theory was subsequently modified by Pang to account for other tissue types and who suggested the term "limited dorsal myeloschisis" to describe aberrant apposition and fusion of the neural folds [45, 57]. The resultant stalk extends from the dysplastic skin to the dorsum of the spinal cord and universally contains neural tissues (peripheral and central) that are "pulled up" into the stalk as the mesenchyme condenses around the early neural tube, interspersed with variable types of mesodermal (or sometimes epidermal, dermal, or even endodermal elements), all encased within a sheath of meningoepithelial cells [57]. Subsequent distention of the track by CSF may create a saccular malformation such as a cervical myelomeningocele [63], meningocele [57, 64], or dorsal myelocystocele [57, 65, 66]. Another author has proposed that cells of the caudal cell mass interfere with caudal neuropore closure, resulting in a sequestrum of cutaneous ectoderm and/or mesenchyme between the cutaneous and neuroectoderm [58]. Aalst described an experimental model in chick embryos in which a segment of newly closed neural tube was reopened and a tiny piece of amnionic tissue was inserted into the breech between the neural folds; 47% of the resultant embryos contained a tissue tract, composed of "strands of fibrotic tissue" and occasionally cysts that extended between the dysplastic skin and the dorsum of the neural tube. However, the tracts did not stain for N-CAM and therefore appeared to lack neural elements, unlike clinical specimens [58]. As the authors state, an alternative explanation is simply that the amnionic tissue was ejected from the neural tube and simply grew within the overlying mesenchyme. To what degree this experimental model accurately reflects the human malformation is therefore unclear.

Premature Dysjunction: Spinal Lipomas/ Lipomyelomeningocelees

The terms spinal lipoma and lipomyelomeningocele have been used interchangeably to describe fatty spinal cord malformations (Fig. 2.11). Some have limited the use of the word lipomyelomeningocele to refer to those malformations in which

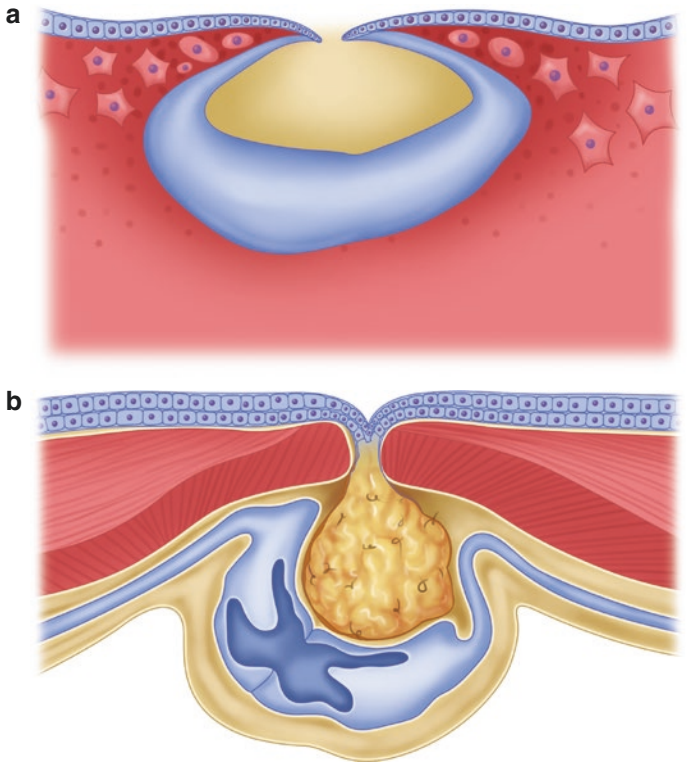

Fig. 2.10 Embryogenesis of dermal and fibrous sinus tracts. (**a**) During normal primary neurulation, the converging neural folds are contiguous with the adjacent and more laterally situated cutaneous ectoderm. As the neural folds meet, they detach from the cutaneous ectoderm (dysjunction) and fuse to form a closed neural tube; the cutaneous ectodermal cells simultaneously fuse to become a continuous epithelium that becomes skin. Mesenchyme will intercalate between the two to form the dorsal muscles, posterior vertebral arches, and mesenchyme. (**b**) A hypothesized failure of dysjunction is thought to underlie the formation of dermal sinus and fibrous tracts. The cutaneous and neuroectoderm remain attached and form a stalk that connects the skin and spinal cord. Surrounding mesenchymal cells aggregate around the tract. (Adapted from Dias and McLone [155])

the fat and/or spinal cord exit the dural sac, while others have lumped all such malformations together. In this chapter, we will simply refer to all of these as spinal lipomas, without making a distinction. Spinal lipomas most frequently arise from the lumbosacral spinal cord, conus medullaris, and filum terminale; some are exclusively intradural but most extend through the dura and involve extradural tissues [67–70]. A number of classification schemes have been proposed [71–73]; the Pang and Morota classifications are probably the most useful from an embryogenetic standpoint. Pang, adding to the Chapman classification, divided lipomas into four types: dorsal, transitional, terminal, and chaotic [72]. The dorsal lipoma arises from the dorsum of the spinal cord, with a normal conus medullaris, and reputedly

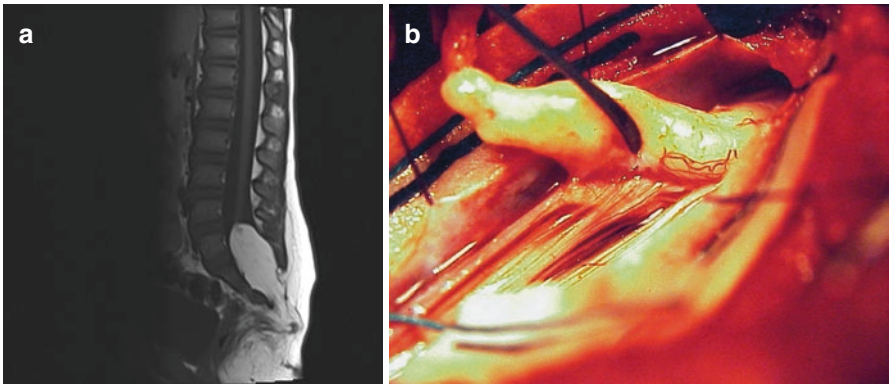

Fig. 2.11 Spinal lipomas. (**a**) Sagittal T1-weighted MRI showing hyperintense lumbar spinal mass. (**b**) Intraoperative photograph showing the relationship of the dorsal nerve roots to the fatty mass

involves an abnormality of primary neurulation. The terminal lipoma involves the filum terminale below the end of the conus and reputedly involves an abnormality of secondary neurulation. The transitional lipoma straddles the two, involving both the dorsum and the terminus of the conus, and likely involves an abnormality of junctional neurulation (the overlap zone between primary and secondary neurulation). Finally, the chaotic lipoma, which is virtually always associated with sacral dysgenesis and/or other caudal abnormalities, likely involves either an abnormality of terminal gastrulation or secondary neurulation. For all but the chaotic types (see below), the displaced neural folds and the dorsal root entry zones are predictably located ventrolateral to the lipoma (Fig. 2.11b); this point is critical to understanding the surgical anatomy of these lesions.

Morota classified spinal lipomas into four types [73]. Their Type I corresponds to the dorsal variety of Pang and was thought to represent an abnormality of primary neurulation. Types II and III correspond to Pang's transitional variety; Type II contains a relatively normal conus ventral to the lipoma and was thought to represent an abnormality of junctional neurulation, whereas Type III contains no normal conus and was thought to represent failed early secondary neurulation. Type IV corresponds to Pang's terminal lipoma and represents an abnormality of late secondary neurulation. Morota did not include chaotic lipomas in their series of 378 spinal lipomas. In support of this classification, associated anorectal sacral and/or urogenital abnormalities were observed in Types II, III, and IV, but not Type I malformations [73].

The long held belief has been that lipomas (at least dorsal/Type I lipomas) also arise through a disorder of dysjunction [74, 75]. In contrast to the dermal sinus tract, in which the cutaneous ectoderm *incompletely* separates from the neural tube, lipomas have been thought to form when the cutaneous ectoderm *prematurely* separates from the neuroepithelium prior to neural fold fusion. Under these circumstances, the surrounding mesenchyme ingresses between the

neural tube and overlying cutaneous ectoderm and gains access to the ependymal surface of the developing neural tube (Fig. 2.12a, b). Whereas mesenchyme adjacent to the outer basal surface of the neural tube is normally induced to form dura, the fate of the anomalous mesenchyme within the central canal may instead be redirected to form fat [75]. Premature dysjunction may occur bilaterally producing a midline mass or unilaterally producing an eccentric mass. The spinal cord in eccentric lipomas is rotated such that the dorsal root zone of the involved side lies dorsal most, nearest the mesenchyme, while the contralateral side lies more ventrally within the canal.

A proposed failure of dysjunction does not account for caudal malformations such as the terminal/Type IV lipomas that involve the end of the conus and/or filum terminale. These lipomas likely take origin from the CCM and represent disorders of secondary neurulation and/or retrogressive differentiation [75, 76]. In support of this concept, the histology of terminal lipomas differs from that of more rostral malformations – the former usually contain only fat cells, whereas the latter more commonly contain striated muscle, mesenchyme, and other disparate tissue types derived from the CCM [75]. The underlying embryopathy that produces both junctional and terminal lipomas is presently unknown. George has proposed that mesenchyme from the regressing primitive streak during gastrulation fails to migrate properly and is instead directed toward, and retained within, the lumen of the developing caudal neural tube where it inhibits neurulation and subsequent dorsal mesenchymal development. These retained cells would lose caudal repressive Wnt signals and respond to lateral mesodermal signals that induce them to form fat. This theory does not require a failure of dysjunction [77].

Disordered Gastrulation: Combined Spina Bifida, Split Cord Malformations, Neurenteric Cysts, and Complex Dysraphic Malformations

A number of seemingly unrelated disorders, including combined (anterior and posterior) spina bifida; split cord malformations; neurenteric cysts; intestinal malrotations, duplications, and fistulae; and a number of other *complex dysraphic malformations* exhibiting disorders of all three primary germ layers, are all thought to have a common embryogenesis, variously described as the "split notochord syndrome" [78], the "endodermal-ectodermal adhesion syndrome" [79], or the "accessory nerurenteric canal syndrome" [80]. The common element in many of these anomalies is a split cord malformation involving some portion of the neuraxis.

Split cord malformations (SCM) arise either in association with open neural tube defects or, more commonly, as occult malformations developing in isolation or in conjunction with other associated anomalies. Early classification schemes have done little to foster our understanding of the embryogenesis of these lesions. Hertwig first used the term diastematomyelia (from the Greek "diastema" meaning cleft and "melos" meaning medulla) to describe malformations in which the spinal

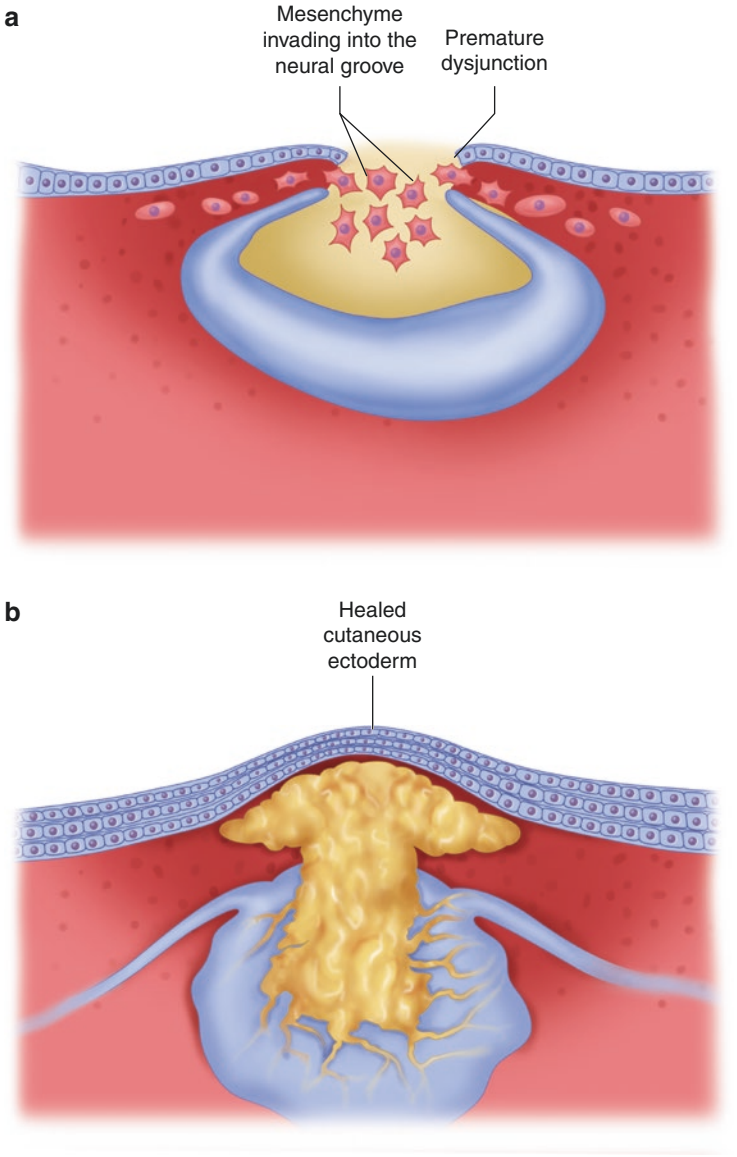

Fig. 2.12 Reputed embryogenetic theory for formation of lipomas. (**a**) Cutaneous and neuroectoderm separate prematurely, allowing surrounding mesenchymal cells to enter central canal where they are induced to form adipocytes. (**b**) The result is a fatty stalk originating within the spinal cord and extending dorsally within the subcutaneous tissues; dorsal roots (derived from the neural folds immediately adjacent to the cutaneous ectoderm) lie ventrolateral to the fatty stalk. (Adapted from Pang [86])

cord was split into two "hemicords," each containing a single set of dorsal and ventral nerve roots. In contrast, Herren and Edwards introduced the term "diplomyelia" to describe a complete duplication of the spinal cord, each side containing *two* sets of ventral and dorsal nerve roots [81–83].

The confusion was further compounded by dividing these malformations according to the composition of their dural coverings or by the presence or absence of tethering midline structures. Each of the "hemicords" in diastematomyelia lay within its own dural sheath, whereas both of the duplicated spinal cords in diplomyelia were thought to be contained within a common, single dural sheath. Midline bony, cartilaginous, or fibrous spurs were present between the two "hemicords" in diastematomyelia, whereas no such midline structures were thought to be present in diplomyelia. Thus, the widespread belief was that diastematomyelia involved a splitting of the spinal cord into two half-cords lying within two separate dural sheaths and separated by an osseous or fibrocartilagenous tethering spur, whereas diplomyelia was thought to involve a true spinal cord duplication within a common dural tube and having no interposed mesenchymal tissue [81, 82].

However, several observations suggest a common embryonic origin for these two malformations. James and Lassman's original description of diastematomyelia includes 11 cases of "single dural tube" malformations, 8 of which contained midline fibrous "bands" analogous to the bony spurs of the double dural tube malformations [84]. These "bands" were also reported by Pang and colleagues (Fig. 2.13). The bands originate in the cleft between the two "hemicords" and traverse the subarachnoid space to end more caudally on the dura; they are composed of tough, fibrous connective tissue and prominent blood vessels (Fig. 2.13d) [85].

Just as the single dural tube malformations of diastematomyelia may have midline fibrous bands, so too may diplomyelia have double dural sheaths and osseous or fibrocartilagenous spurs. Herren and Edwards described several cases of "diplomyelia" with such midline spurs, and both double and single dural tube malformations were described with approximately equal frequency [82].

Finally, dystrophic median nerve roots, projecting from one or both "hemicords" and inserting onto the midline osseous spurs or fibrous bands, have been described in both diastematomyelia and diplomyelia [82, 84–87]. Both dorsal and ventral roots, as well as ganglion cells, have been described (Fig. 2.13e) [85, 87]. The presence of both lateral and median sets of nerve roots arising from each "hemicord" strongly suggests the presence of at least a partial spinal cord duplication in both malformations. Moreover, illustrations of the "hemicords" from published examples of both diastematomyelia and diplomyelia demonstrate neither absolute splitting nor complete duplication of the cord in any instance. Rather, the "hemicords" are *incomplete duplications*, with relatively well preserved lateral halves and dystrophic medial halves (Fig. 2.14) [81, 82, 87–89].

These observations suggest that diastematomyelia and diplomyelia represent different ends of a spectrum of split cord malformations sharing a common embryonic origin; the anatomical differences are due to the subsequent fates of various

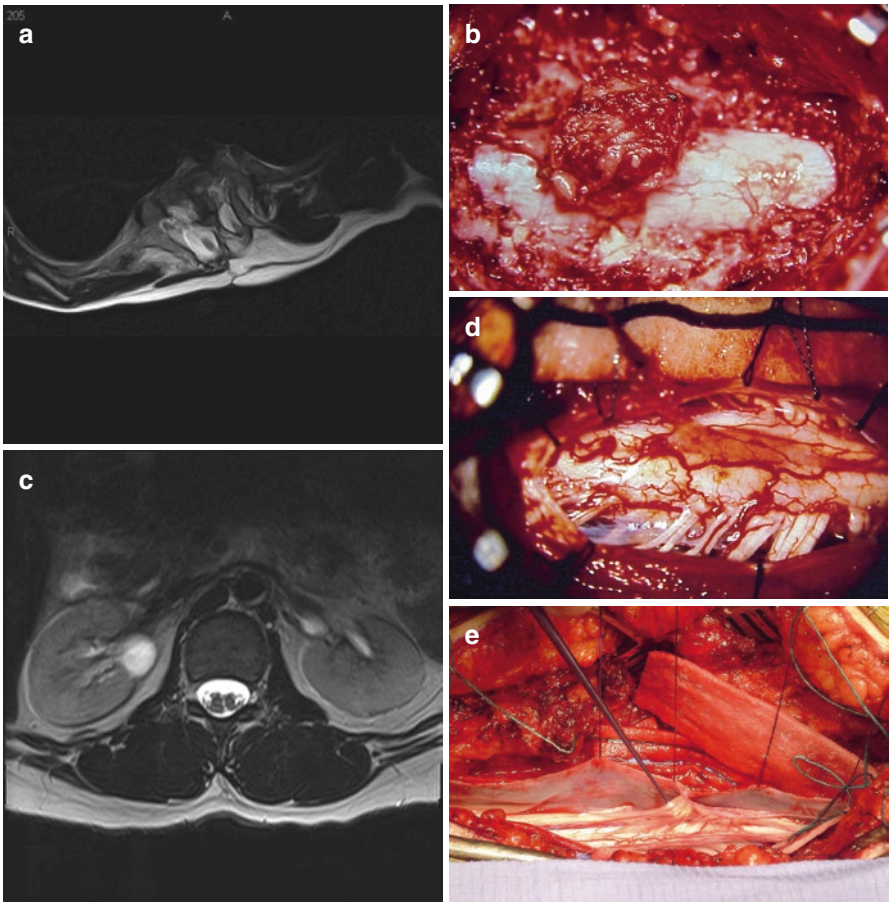

Fig. 2.13 Split cord malformations (SCM). (**a**) Axial T2-wighted MRI demonstrates a Type I SCM, with two hemicords contained within two separate dural sacs and an intervening extradural bony spike. (**b**) Intraoperative photograph in another case showing an extradural bony spike projecting through the dura. (**c**) Axial T2-weighted MRI demonstrates a Type II SCM, with two hemicords contained within a single dural sac. No intervening tethering bands are visible in this MRI. (**d**) Intraoperative photograph showing two hemicords within a single dural sac with a dorsal fibrous band (sail) of tissue connecting the two hemicords to the dorsal dura. (**e**) Intraoperative photograph in another case showing a Type II SCM with several median nerve roots projecting to the overlying dorsal dura (meningocele manqué)

tissue types. Split cord malformations are seen in association with a variety of anomalies including combined (anterior and posterior) spina bifida (Fig. 2.15); hemimyelomeningoceles; myelomeningoceles (occurring in up to one-third of autopsied cases); cervical myelomeningoceles; neurenteric cysts; some examples of the Klippel-Feil anomaly, iniencephaly, and caudal agenesis; and certain intestinal duplications and diverticulae. All of these *complex dysraphic malformations* have in common stereotypical anomalies involving tissues derived from all three

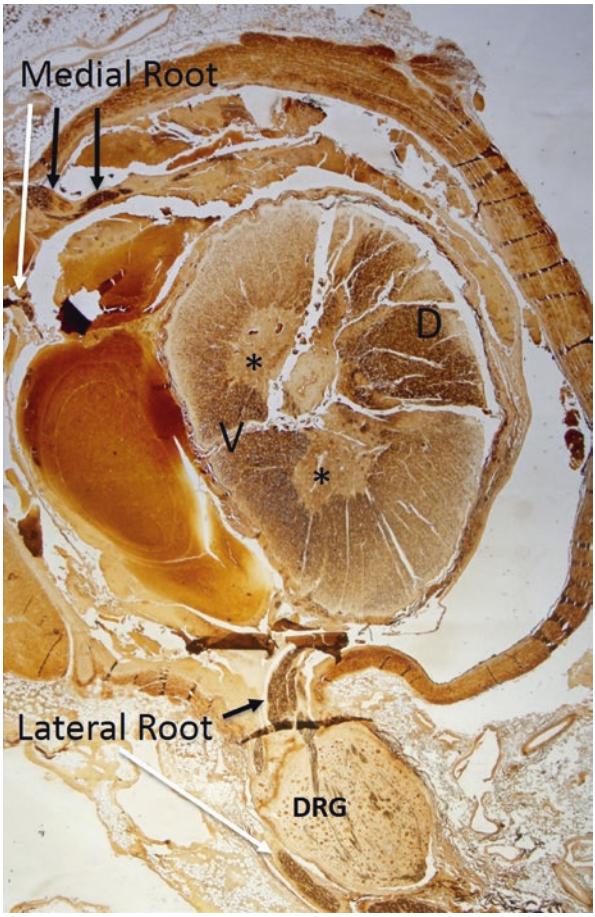

Fig. 2.14 Photomicrograph of one hemicord in a patient with a split cord malformation. The figure demonstrates well developed ventral horns (*) as well as both medial and lateral dorsal (black arrows) and ventral (white arrows) roots as well as a dorsal root ganglion (DRG) associated with the lateral dorsal root. The medial set of roots were traveling toward a bony midline septum (not shown but located toward the left of the figure)

primary germ layers and are thought to share a common embryonic origin [90, 91]. Four theories have attempted to explain the underlying embryopathy:

1. Beardmore and Wigglesworth [92] proposed that prior to or during notochordal outgrowth, an adhesion could develop between the epiblast and hypoblast. This "endodermal-ectodermal adhesion" would provide a barrier to subsequent notochordal elongation and result in a splitting of the notochord around the adhesion; independent development of paired neuroepithelial anlagen would then

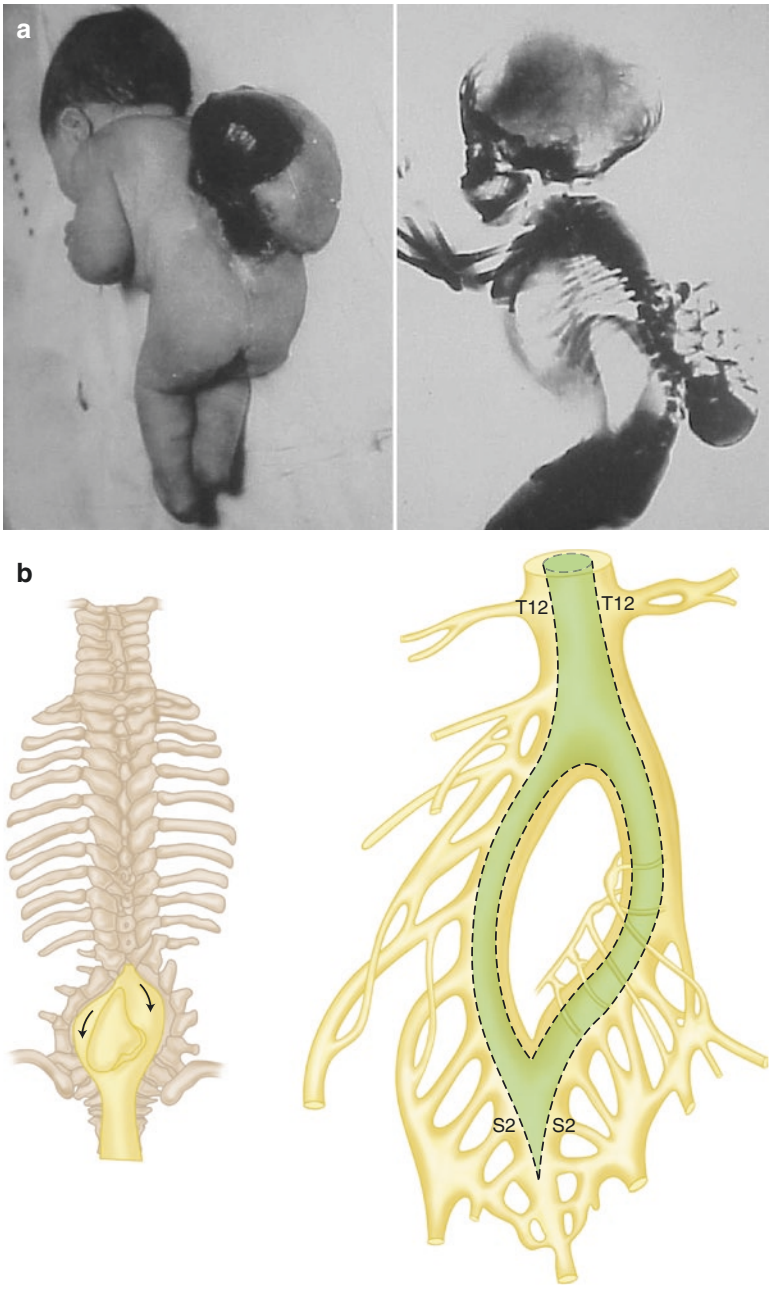

Fig. 2.15 Combined (anterior and posterior) spina bifida. (**a**) *Left*, infant with a large dorsal sac. *Right*, radiograph demonstrating bowel within the dorsal sac, with essentially no bowel within the peritoneum. (**b**) *Left*, diagram showing split in bony vertebral column. *Right*, diagram showing corresponding split in spinal cord. ((**b**) Adapted from Saunders [95])

form two "hemicords." Associated remnants of the adhesion could give rise to endodermal remnants located anywhere between the gut and cutaneous ectoderm. This mechanism could work only if the notochord extends cranially from Hensen's node; if, on the other hand, the notochord grows by addition of cells to its caudal end during Hensen's node regression, an adhesion of this type would not provide a barrier to notochordal outgrowth. Prop et al. [79] have consequently modified this theory by postulating an adhesion within the primitive streak caudal to Hensen's node, around which the notochord might be split during node regression.

2. Bremer [80] studied patients with combined spina bifida (or the "split notochord syndrome"), characterized by a posterior sac and widespread underlying vertebral anomalies (Fig. 2.15). The involved vertebrae are split midsagittally, forming two "hemivertebral" columns that surround a central cleft; a Type I split cord malformation is present with two "hemicords," each within its own dural sac, surrounding the central cleft. Tissue (ranging from endodermal cysts to entire loops of bowel) from the peritoneal cavity passes through the central cleft and is present within the dorsal sac. Associated visceral malformations include intestinal malrotations, diverticulae, or duplications [92, 93].

   Bremer noted the similarities between the central cleft in combined spina bifida and the neurenteric canal of normal embryos. However, the dorsal opening of the neurenteric canal is the primitive pit, which ultimately is located at the tip of the coccyx, whereas combined spina bifida (and other variants of SCMs) involves more cranial levels of the neuraxis. Bremer therefore proposed that such malformations involved the formation of an "accessory neurenteric canal" caused by a dorsal herniation of endoderm that splits the notochord and neuroepithelium. However, the mechanism by which such a dorsal herniation occurs was not further clarified.
3. McLetchie [94] and Saunders [95] suggested that the initial abnormality involves a notochordal duplication and is followed by a secondary permissive endodermal-ectodermal interaction between the duplicated notochords. Dodds [96] suggested that, during normal embryogenesis, bilaterally paired prospective notochordal cell anlagen might be integrated into a single midline structure during primitive streak regression. Feller and Sternberg [97] proposed that abnormal rests of undifferentiated cells in Hensen's node might interfere with proper midline integration and result in paired notochords between which these cell rests give rise to a variety of midline tissues derived from any of the three primary germ cell layers.
4. Dias and Walker [90] proposed that SCMs and other complex dysraphic malformations arise during a time when prospective anlagen from all three germ layers are being laid down during *gastrulation* (Fig. 2.16). During normal development, paired notochordal anlagen in Hensen's node are integrated into a midline notochordal process, while prospective neuroepithelial cells flanking either side of Hensen's node and the primitive streak are integrated to form a single midline neural plate. To form complex dysraphic malformations, there is failure of

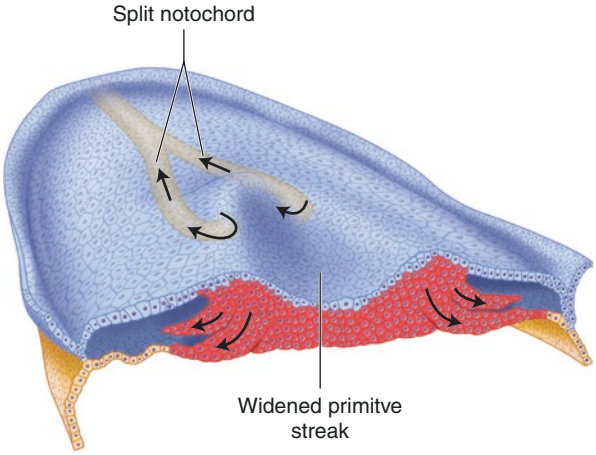

Fig. 2.16 Embryogenetic theory for the origin of split cord malformations and other related malformations as a consequence of disordered gastrulation (Dias and Walker). Hensen's node is altered, resulting in disrupted midline axial integration. Two "heminotochords" are laid down, and the surrounding neural plate is induced to form two relatively independent "hemi-neural tubes." The intervening cells, derived from multipotent cells in Hensen's node, may develop into a variety of both normal and abnormal tissues between the two resultant "hemicords" such as neurenteric cysts, ectopic ovarian or renal tissues, Wilm's tumor or teratomas. (Adapted from Dias and Walker [90])

proper midline integration of both the notochordal anlagen and adjacent prospective neuroepithelium, allowing them to develop independently over a portion of their length to produce a split notochord and paired "hemicords." Laterally displaced and malformed somites would form an abnormally widened spinal canal with associated vertebral segmentation anomalies including sagittally clefted ("butterfly") vertebrae, fused vertebrae, hemivertebrae, absent vertebrae, or, if displaced widely enough, partially duplicated vertebral columns as seen in combined spina bifida. The intervening space between the paired "hemicords," comprised of pluripotent primitive streak cells, could give rise to a variety of normal or abnormal tissue types from any of the three primary germ layers, including enteric structures (neurenteric cysts; loops of bowel), mesenchymal tissues (the bony or fibrous midline structures, blood vessels, muscle and fat encountered in SCMs; anomalous vertebrae; immature renal tissues) and ectodermal tissues (dermoid and epidermoid tumors), and even teratomas and Wilm's tumors [98–100].

Similar malformations have been reproduced in chick embryos by splitting Hensen's node midsagittally into two "heminodes" during gastrulation. Double neural tube malformations of variable extent are produced by these maneuvers and are associated with widespread open neural tube defects and multiple somitic

abnormalities. Splitting the node during mid-gastrulation (when the primitive streak is at full extension) produces more cranial malformations, whereas manipulations performed slightly later, during primitive streak regression, result in more caudal malformations [90]. These malformations were produced in amphibian neurulae embryos by similarly disrupting the neural plate and endoderm [101, 102]. These data support the theory that complex dysraphic malformations could be the result of disordered gastrulation, although the exact embryopathy remains to be elucidated. One possibility is that a deficiency of the basement membrane underlying the neuroepithelium immediately lateral to the primitive streak allows independent ingression of separate notochordal precursors and the establishment of independent neural tubes. Another possibility is that abnormal epithelial to mesenchymal transition involving medical node-streak border cells during junctional neurulation retains their mesenchymal differentiation and separates the more lateral neural folds. However, the latter mechanism doesn't explain SCM and other complex malformations located cranial to the thoracolumbar junction (where junctional neurulation occurs).

Disorders of Secondary Neurulation: Terminal Myelocystocele

Abnormalities of secondary neurulation are thought to produce only skin-covered malformations, since secondary neurulation occurs beneath an intact cutaneous ectoderm. Since the sacral spinal cord segments (below S2) and filum terminale are the only parts of the nervous system to develop from the caudal cell mass [103], disorders of secondary neurulation produce malformations which involve only these caudal most structures. Common malformations include disorders of the filum terminale (including terminal lipomas) and terminal myelocystocele. The embryopathy leading to the shortened or fatty infiltration of the filum is entirely unknown but may represent abnormal secondary neurulation (as discussed above under terminal lipomas) or of retrogressive differentiation.

Terminal myelocystoceles (Fig. 2.17) are rare occult dysraphic lesions in which the central canal of the caudal spinal cord dilates to become a CSF-containing, glial, or ependyma-lined terminal cyst (or myelocystocele) [104, 105]. The dilated terminal cord is surrounded, in turn, by a dilated and ectatic dural sleeve. This produces a "double sac" in which the contents of the inner sac communicate with the central canal of the more cranial spinal cord, while the contents of the outer sac communicate with the more cranial subarachnoid space [105]. Ordinarily, there is no free communication between the inner and outer sacs [105]. An associated lipoma is almost universal. Malformations of other caudal organ systems (all derived from the caudal cell mass) are frequent [104–106] and include cloacal exstrophy, imperforate anus, ambiguous genitalia, and multiple caudal vertebral malformations including segmentation anomalies and caudal agenesis. Myelocystoceles are one component of the OEIS complex (omphalocele, exstrophy, imperforate anus, and spinal malformations) [106].

Terminal myelocystoceles are thought to arise from the CCM during secondary neurulation [104, 105, 107]. The juxtaposition of cells in the CCM that give rise to

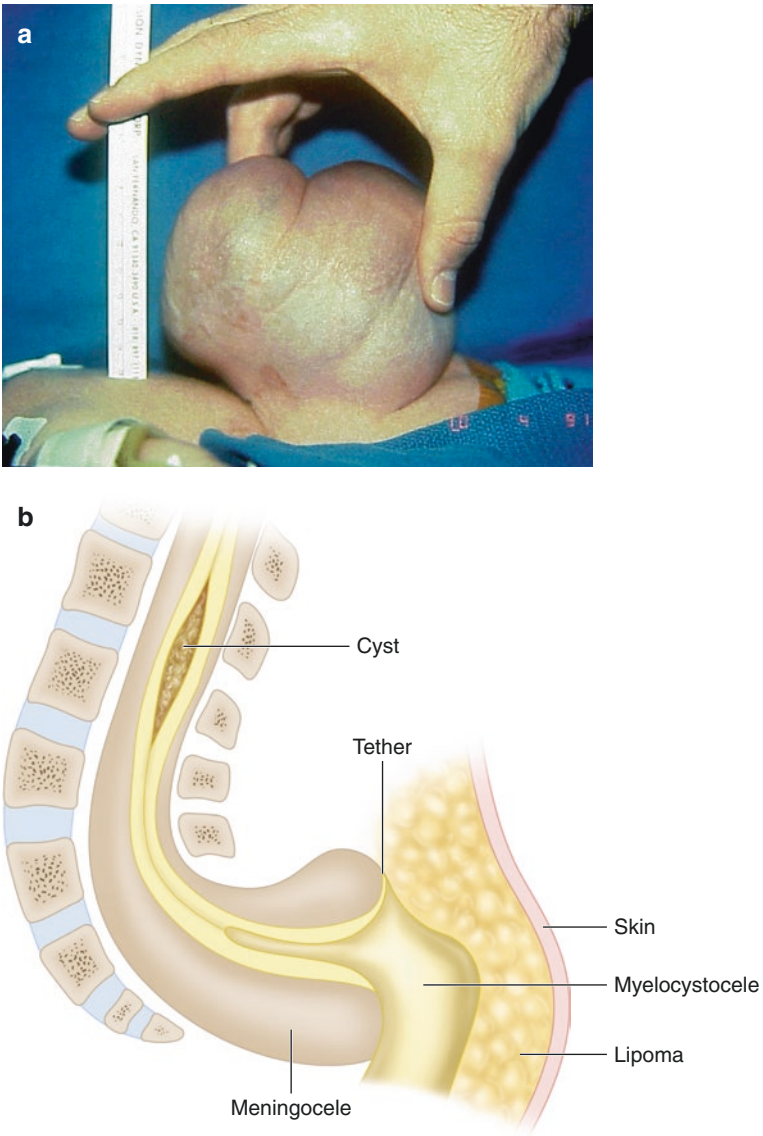

Fig. 2.17 Myelocystocele. (**a**) Clinical photograph showing a huge skin-covered sac. (**b**) Illustration showing myelocystocele containing a dilated terminal central canal projecting into a larger dilated terminal dural sac. A lipoma is also present caudal to the malformation. ((**b**) Adapted from McLone and Naidich [105])

multiple organ rudiments probably accounts for the almost universal association of myelocystocele with other hindgut and cloacal anomalies [105]. An early proposal is that CSF, unable to exit from the central canal, is vented into the terminal portion of the central canal during canalization of the secondary neural tube [105], assuming that the central canals of the primary and secondary neural tubes are in

continuity during canalization, as occurs in the mouse [13]. Alternatively, CSF could distend the terminal neural tube secondarily after its formation and integration with the cranial neural tube. Progressive accumulation of fluid would then distend the central canal, and continued growth of the terminal cyst would distend the surrounding arachnoid and produce the enveloping outer sac. Finally, the cyst ultimately disrupts the overlying mesenchyme (but not the cutaneous ectoderm), producing a dorsal bony dysraphism and mesenchymal abnormality with intact overlying skin [105].

The nature of the underlying CSF disturbance is uncertain. The absence of hydrocephalus in most patients with terminal myelocystoceles suggests that the disturbance in CSF dynamics is probably local rather than global. More recently, Pang and colleagues have described a stage of normal neurulation in the chick embryo, after the coalescence of the primary and secondary neural tubes, in which the terminal central canal enlarges progressively into a caudal balloon-like structure with only a thin overlying skin. This terminal dilation later collapses. Pang has noted the similarity between this embryonic dilation event and the appearance of the terminal spinal cord in myelocystoceles and has proposed that myelocystoceles arise as a result of an arrest at this stage of development [108, 109].

Anomalies Resulting from Failure of Caudal Neuraxial Development: Caudal Agenesis

The term caudal agenesis was suggested by Passarge and Lenz [110] in 1966 to describe a group of caudal malformations characterized by a partial or complete absence of a variable number of lumbar and/or sacral vertebrae, together with corresponding regions of the caudal neural tube. The vertebral anomalies are striking (Fig. 2.18); in addition to agenesis, other complex vertebral anomalies may be present cranial to the absent regions and include hemivertebrae, wedge-shaped vertebrae, fused vertebrae, sacralization of lumbar vertebrae, posterior spina bifida, midline bony spurs, and abnormal rib articulations [111–118]. In some cases, bizarre, complex vertebral anomalies are present. The spinal canal is sometimes widened; in the extreme, combined spina bifida occurs [91, 119–121].

The distal spinal cord is absent (Fig. 2.18), with the terminal spinal cord ending in a dysplastic glial nodule [112, 122, 123]. Motor deficits usually correspond to the level of the agenesis. In contrast, sensory sparing is characteristic [113, 114, 116–118, 121, 124–127], suggesting a relative preservation of neural crest cells; alternatively, migration of neural crest cells from more cranial spinal segments may occupy the territory rendered vacant by the agenesis. Associated myelomeningoceles are present in up to 50% of cases [116, 118, 125]; conversely, sacral agenesis is reported in up to 24% of patients with myelomeningoceles [128]. Split cord malformations (both single and double dural tube malformations) have been reported in several patients [116, 121, 129–131].

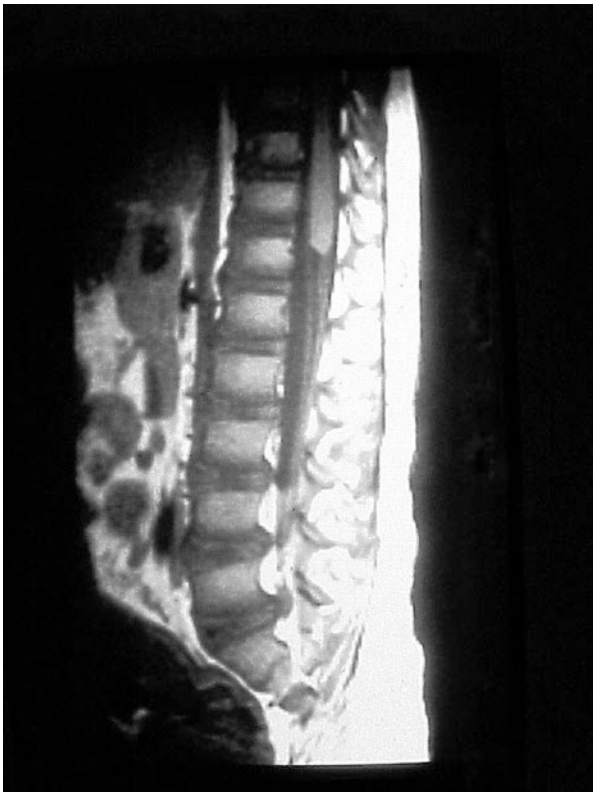

Fig. 2.18 Sacral agenesis. Sagittal T1-weighted MRI showing absence of much of the sacrum, with a blunted conus medullaris that is missing the portion presumably formed from secondary neurulation

Associated limb anomalies are common and include flattened buttocks, gluteal atrophy, and equinovarus deformities. The legs are wasted distally, imparting an "inverted champagne bottle" appearance [115]. Histologic examination of involved muscles demonstrates a virtual absence of myocytes with relative preservation of connective tissues [112, 117, 122, 123] and suggests either denervation atrophy [115, 127] or a failure of somitic development to contribute myoblasts to prospective muscle masses.

Associated visceral malformations are present in 35% of patients with caudal agenesis [113] and most commonly include intestinal (tracheoesophageal fistulae, Meckel's diverticulum, cloacal exstrophy, omphalocele, intestinal malrotations) and urogenital (renal agenesis, horseshoe kidney, ureteral and bladder duplications, anomalies of external genitalia) malformations [116, 117, 120, 123, 127, 132, 133]. Currarino's triad is a disorder involving a triad of sacral dysgenesis (usually a hemisacral or *scimitar* sacrum), an anorectal malformation, and an anterior sacral mass, most commonly an anterior sacral meningocele or a presacral teratoma [134–136]. It is inherited in at least 50% of cases,

and autosomal dominant, recessive, and X-linked patterns have been described [137–140].

The etiology of caudal agenesis is not completely known, although most authors agree that the malformation arises during early embryogenesis, likely around POD 16, and involves the early formation of the notochord from the CCM [140]. The association of caudal agenesis with myelomeningoceles certainly suggests a disorder that arises prior to or during caudal neural tube closure. The frequent occurrence of caudal agenesis in offspring of diabetic mothers is well described [110, 122, 124, 141]. "Rumpless" chickens exhibiting similar malformations have been produced by exposing embryos to insulin or other sulfur-containing compounds during early embryogenesis [142–144]. Similar malformations have been produced in mice by exposing embryos to hyperglycemic medium or to ß-hydroxybutyrate, a ketone body which is elevated during periods of ketoacidosis [145]. The optimum time for producing such anomalies is during late gastrulation, when caudal neuraxial structures are first being formed. Sadler and colleagues have invoked an interference with the structure and/or function of glycoproteins known to be involved in early embryonic development [145].

Duhamel has proposed a common etiology for a wide spectrum of malformations involving the caudal urogenital and gastrointestinal systems, including imperforate anus at the one extreme, to sirenomelia (in which there is caudal spinal agenesis, multiple visceral anomalies, and associated fusion of both hind limbs into a single appendage – the so-called "mermaid" syndrome) at the other; caudal agenesis is thought to comprise an intermediate form of these disorders [146]. Sirenomelia has been produced in chickens by destroying the caudal axial mesoderm [147], which has led to the suggestion that a disorder of an axial mesodermal "developmental field," which is responsible for orchestrating the migration and determination of prospective caudal mesodermal cells during gastrulation, might be responsible for caudal agenesis. According to this theory, malformations arise when epiblast cells migrating through the primitive streak "…fail to make, at the proper time, the proper transition whereby they come to acquire mesodermal characteristics" [148]. A caudal "organizer" has been implicated by others in the pathogenesis of caudal agenesis [113, 116, 149]. Such a "developmental field" or "organizer" is thought to act through cell-cell interactions mediated by cell surface "morphogenesis proteins" [148, 150]. The association of caudal agenesis with the broader group of malformations collectively referred to above as "complex dysraphic malformations" and having split cord malformations suggests that caudal agenesis may perhaps represent another expression of a disorder of midline axial integration during gastrulation [90].

The autosomal dominant form of Currarino's triad has been mapped to a mutation in the homeobox gene HLXB9 on chromosome 7, although the mutation may be necessary but not sufficient to produce the malformation, and its exact role is unclear [140]. More recent studies (reviewed in Fontanella [151]) have implicated the T (brachyury) gene in the genesis of a number of caudal malformations including sacral agenesis. A recent report of four fetuses with a mutation of the T gene demonstrated a number of congenital malformations including sacral agenesis; all

four fetuses had persistent complete notochord extending the entire length of the spine with malformations of the vertebral bodies [151].

Disorders of Retrogressive Differentiation or Apoptotic Cell Death: Retained Medullary Cord

A rare but embryologically important malformation is the "retained medullary cord," described by Pang [152]. In this malformation, the caudal spinal cord extends to the end of the thecal sac, with associated nerve roots exiting from the spinal cord adjacent to each lumbar, sacral, and even coccygeal level and without a filum terminale (Fig. 2.19). Pang proposed that this "retained medullary cord" reflects a partial or complete arrest of neural development that prevents normal retrogressive differentiation, perhaps related to aborted apoptosis, leaving the distal spinal cord intact without a filum [152].

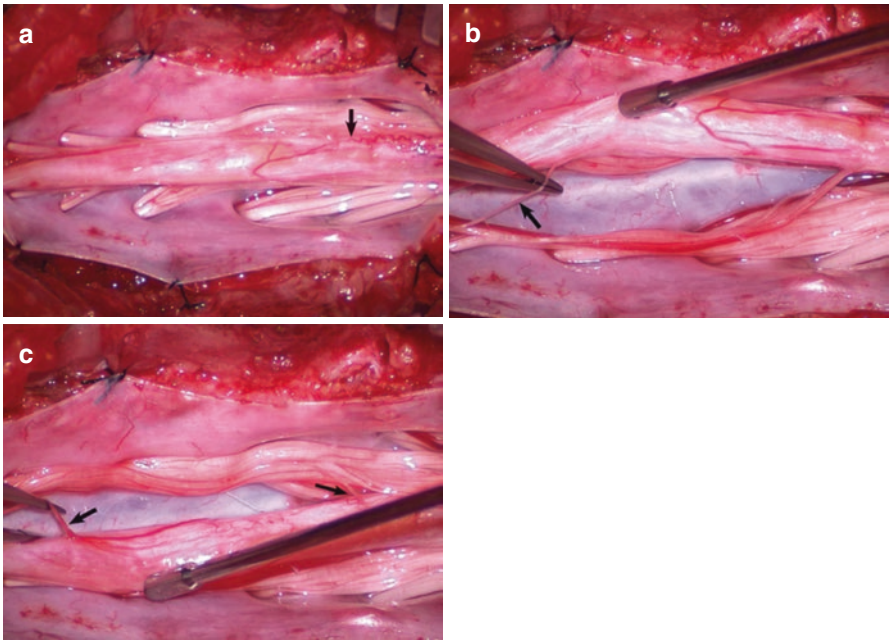

Fig. 2.19 Retained medullary cord; intraoperative photograph. (**a**) Thick, pia-covered spinal cord-like structure, the medullary cord, extends down to the end of the dural sac. The wriggly surface vessel at the rostral (conus) end that suddenly becomes straight (arrow) is the site where direct cord motor mapping confirmed the beginning of the medullary cord. (**b**, **c**) Show small nerve roots (arrows) emanating from right and left sides of the medullary cord. (From Pang et al. [152]; with permission)

Conclusion

A thorough understanding of embryology provides a solid background for the accurate diagnosis and rational treatment of children with dysraphic malformations. We have reviewed normal development in considerable detail and discussed the current state of knowledge regarding the mechanisms underlying dysraphic spinal malformations. As we have seen, a variety of theories have been offered to explain the origin of these malformations; some have advanced our understanding of dysraphism, while others have fallen short of the mark. It is important to understand that although these are plausible theories, few have been rigorously tested experimentally, and none have been proven. The recent explosion of knowledge about the cellular and molecular determinants of development will almost certain advance our knowledge about how dysraphic malformations occur on a molecular and genetic level. Armed with a knowledge of normal embryonic mechanisms, the next generation of pediatric neurosurgeons is poised to provide some answers to the many unanswered questions that remain.

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Natural History of Occult Spinal Dysraphism

3

Jeffrey P. Blount and Zachary G. Wright

Abbreviations

DST	Dermal sinus tract
OSD	Occult spinal dysraphism
SCM	Split cord malformation
TCS	Tethered cord syndrome

Introduction

The natural history of OSD is the central issue impacting surgical decision-making in occult dysraphism. Only by comparing surgical risks to the natural history of the untreated illness can a rational, informed decision be made for or against surgical intervention. While the detailed natural history of the three broad forms of OSD (lipoma, DST, SCM) remains incompletely understood, the overall clinical pattern appears dominated by the tethered cord syndrome (TCS). There is some controversy surrounding whether TCS is the sole or a dominant contributor to clinical decline in patients harboring an OSD, but there is consensus that it is a potentially treatable important contributor in many OSD patients.

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Background

During the 1950s, papers described neurological decline over time associated with occult dysraphism, but it was not until the 1970s that surgical procedures were developed and widely performed that attempted to disrupt the tether and arrest such decline [1–4]. Patients harboring OSD defects were found to show neurological disability that generally correlated with age for the first two decades of life [5, 6]. This recurring observation in multiple series prompted the concept of reversible decline arising from progressively severe tethering of the spinal cord [5–9].

Patients who presented with neurological findings demonstrated arrest of decline and even modest improvement following surgical untethering in multiple large clinical series [5, 6, 10–14]. An improvement in pain and cessation of neurological decline were observed in many symptomatic patients regardless of the type of occult defect present. Despite confounders and methodological limitations to these studies, a period of robust enthusiasm ensued for the concept of TCS and the effectiveness of surgery in disrupting it [10, 15–17]. Patients with symptoms showed good response to surgery but more overall neurological disability than those who were operated upon before symptoms developed [7]. This was widely interpreted as demonstrating the importance of early surgery, and enthusiasm for prophylactic surgery and early referral increased [6, 7]. It became generally accepted that asymptomatic occult lesions were associated with inevitable decline and that surgical untethering was the best way to prevent this and the associated loss of function and independence [6, 7, 16, 18, 19].

Over time, the long-term effectiveness of surgery in preventing decline from TSC became less clear [20, 21]. A disconcerting number of patients with lipomas demonstrated signs and symptoms of recurrent TSC following prophylactic untethering [21, 22]. This called into question the long-term effectiveness of surgical untethering in protecting against neurological decline related to tethering. Some groups found that lipoma patients who were serially examined without surgical intervention demonstrated stable neurological exams or nearly imperceptible rates of decline [23]. This prompted a reassessment of the inferred natural history that had been accepted, and several groups adopted and advocated a more conservative approach toward asymptomatic patients with lipomas [20, 24, 25]. Understanding of the natural history of OSDs remains controversial and is of great practical surgical relevance since it shapes the fundamental approach to prophylactic surgery and its role. Since most children are screened by pediatricians and are referred for any cutaneous anomaly involving the lumbar region, this is the most common clinical scenario and as such has great practical importance.

Overview of the Natural History of OSD

While there is general consensus among experienced observers that tethering is important in the decline of patients with OSD, there is disagreement about its relative contribution and its variability in asymptomatic patients [20, 22]. Furthermore, there are pronounced disparities in opinion among highly experienced, thoughtful

investigators with regard to the aggressiveness of resection of tethering lesions [14, 16, 23]. Much is uncertain and there can be confusion. A clear summary of central principles and areas of uncertainty and future investigation is worthwhile:

Established Principles of the OSD Natural History

1. Progressive neurological decline of the lower extremities and bladder/bowel during the first two decades of life is a real and predictable phenomenon for most patients who harbor a form of OSD [5–7, 13, 22].
2. Patients may show different rates and extents of decline and up to slightly less than half with asymptomatic lipomas may decline only modestly over time or demonstrate clinical stability [20, 23, 24, 26]. Split cord malformations may similarly show some variability in decline that is currently less well established [12, 15, 18, 27].
3. The loss of neurological function is typically not recovered [5, 9, 12, 22, 28].
4. Decline is often subtle and occurs over multiple domains (motor, sensory, pain, bladder reflexes, etc.) that vary between patients [10, 17, 20, 22, 28]. A useful classification of clinical patterns of decline has never been developed.
5. Objective measures of lower extremity function or the status of neuro-urological health are lacking. Current measures are imperfect and subject to interpretation and subjectivity [14, 22, 24].
6. Surgical intervention for patients with symptoms seems to help [5, 18, 22, 27–29]:
   - Pain is improved most reliably.
   - Neurological decline is arrested at least transiently, but lost function rarely improves or returns.
   - Recurrent late decline occurs in a significant percentage of patients with lipomas who undergo surgery via traditional surgical approaches (sub-total placode reconstruction).
   - Despite limitations in metrics, patients who are carefully followed with multidisciplinary assessments do better than those who are lost to follow-up.

Central Questions Regarding the Natural History of OSD

1. To what extent are variations in clinical natural history due to the following?
   - Pathological anatomy
   - Phenotypic expressions of subtle genetic differences (molecular subtype analysis and classification) between different types of tethering mechanisms
   - Epigenetic phenomena such as activity, obesity, BMI, diet, metabolism, diet or toxin exposure
2. Is the fundamental event in the pathogenesis of tethered cord related to:
   (a) Longitudinal stress imparted by growth?
   (b) Fixation with micro-trauma from repeated movements of normal living?
   (c) Absorption of the pulsatile force of a large blood volume with systole?

3. How variable is the rate of decline and do different tethering lesions result in similar rates of neurological decline?
4. Are the lesions that show clinical progression different in some definable way from those that show clinical stability?
5. Is the mechanism of decline in recurrent cases of tethered cord the same as that for initial de novo tethered cord?
6. Are radical resection techniques of lipoma resection (advocated by Pang and colleagues) widely applicable/achievable in a diverse and broad community of pediatric neurosurgery?

Natural History of Dermal Sinus Tracts

Congenital dermal sinus tracts are thought to arise from focal failure of disjunction between the neuroectoderm and cutaneous ectoderm during the first trimester [1, 22, 30, 31]. The result is a focal tract between the skin and underlying neural structures. The clinical spectrum is wide, but this lesion threatens neurological well-being as (a) a source of tethering and (b) a potential conduit between the subarachnoid space and the external world. Thus, it can cause decline from TSC or can potentiate bacterial meningitis [1]. DSTs have been reported on the midline along the entire length of the neuraxis from the nose to the sacrum, but the overwhelmingly most common location for this rare lesion is over the lumbar or lumbosacral regions [1, 30]. Critical characteristics that distinguish DSTs from sacral pits include skin origination within the gluteal crease, termination within the central nervous system, lining with stratified squamous epithelium, and other concomitant cutaneous anomalies [1, 30]. Because these lesions entail a real and well-understood risk of infection, they are virtually always removed [22]. Therefore, the natural history of untreated dermal sinus tracts has never been comprehensively studied or reported in the modern era. However, historical studies show that untreated DST could give rise to a wide range of infections including meningitis and focal abscesses [1, 31]. Virtually all of these reports are case reports or limited small series, so the natural history and exact incidences of comorbidities complicating DST have never been calculated. However, from a practical perspective, natural history is a less important issue because DSTs present a real risk of recurrent meningitis [22]. Their surgical removal is low risk, and virtually all that are diagnosed are surgically removed in North America [1, 22, 30].

Natural History of Split Cord Malformations

SCMs are rare forms of closed dysraphism characterized by division of the spinal cord into either a single cord divided by a septum (type I, previously diastematomyelia) or formation of two hemi-cords variably interrupted by a fibrous or bony septum (type II, previously diplomyelia) [3, 11, 15, 27, 29]. The embryo-pathogenesis is uncertain, and various hypotheses have been proposed. Previously, the terms

diplomyelia and diastematomyelia were used inconsistently and occasionally interchangeably, precluding historical contributions to specific natural history studies [12, 18, 32]. Collectively and from a practical surgical perspective, the various forms of SCM are strongly associated with TCS and therefore potentially surgically amenable to improving an otherwise threatening natural history. In a true split cord (SCM I), tethering can occur via either a perforating bony or cartilaginous spicule, the associated thickened arachnoid bands, or by the medial dural sleeve that can envelop the perforating spur [15, 18, 29]. There are too few series for the natural history of these lesions to have been established. However, recurring observations are similar to other tethering lesions. Guthkelch was an early proponent of observation in an effort to avoid harm [3]. Early patients were observed and deteriorated neurologically, while later patients were operated upon "prophylactically" and retained normal function [3]. These observations established a consensus for the central role of tethering in the pathophysiology of SCMs and the inferred ominous natural history of the untreated condition.

More recent studies have suggested other possible contributors to the pathophysiology. Andar and colleagues concluded from studying a cohort of 47 patients with split cord anomalies that the "neuro-orthopedic syndrome" characterized by sensory-motor dysfunction and lower limb asymmetry was a consequence of abnormal functional anatomy and was minimally amenable to surgical improvement [27]. Neurological and "neuro-ortho" findings were common, but true progression of symptoms was rare. Surgical untethering for true progression was effective in arresting but not reversing the observed declines [27]. Thematically, this is similar to other examples of TSC from OSD. Early observations of decline in patients harboring potentially tethering lesions supported a fundamentally essential role for surgery in arresting ongoing decline. Greater experience modestly tempered these inferences by enhancing awareness that each of these dysraphisms is a complex lesion with inherently disordered embryogenesis and resulting disordered neuroanatomy. Tethering appears to be an important potential contributor but is unlikely to be the only one. Consequently, surgical untethering is contributory but can neither reverse deficit nor prevent all neurological impairment.

Natural History of Spinal Cord Lipomas

Lipomas are the most common form of OSD and consist of fat and fibrous masses that invade and tether the spinal cord [6, 25, 33]. They are comprehensively discussed in Chap. 11 and will be considered briefly here with particular regard for their natural history. Lipomas of the filum (Chap. 8) (filar lipomas) minimally invade the neural structures but can cause tethering of the spinal cord irrespective of whether the position of the conus medullaris is abnormally caudal [2, 10, 21, 33]. The natural history of these lesions has never been studied in detail, but they are observed in 5% of otherwise normal lumbar MRIs [33]. It therefore seems that a substantial percentage of these lesions never cause symptoms and require no intervention [21, 33]. It has been inferred that robust thickened fila with fatty infiltration

show characteristic decline associated with TCS, particularly if the conus is abnormally caudal in position [2, 4, 17]. In virtually all surgical series, surgical clipping of the fat-infiltrated filum in patients with symptomatic TCS is associated with reduction or dissipation of pain, cessation of neurological decline, and minimal operative morbidity. The entity of TCS with conus in the normal position has been described and debated and is developed elsewhere in this book (Chap. 8). The natural history of this entity is unknown.

Lipomas of the conus are markedly more complex. They are anatomically very variable and can be challenging both for clinical decision-making and technical performance of the resection/untethering. Dorsal lipomas invade directly into the dorsal surface of the conus and spare the exiting nerve roots. In contrast, caudal and transitional lipomas incorporate the distal caudal surface of the conus, which involves the exiting nerve roots in the fat mass [6, 14, 16, 17]. These challenges and the resultant potential for iatrogenic neurological injury have prompted many neurosurgeons to adapt a limited approach to fat removal. In a conventional resection for a conus lipoma, fat is removed to enable debulking and enlargement of the surrounding dural sleeve, but aggressive resection at the interface between fat and spinal cord is not pursued [6]. An alternative approach prompted by dissatisfaction with the rates of recurrent tethering incorporates a more radical resection of fat and reconstruction and expansion of the dural sleeve to prevent re-tethering [8, 25]. Radical resection and reconstruction of the dural sleeve shows better progression-free survival from neurological decline but has been embraced in a limited way owing to its inherent technical challenges and risks of dissecting at the interface between the lipoma and the conus medullaris.

The natural history of lipomas is widely considered to represent TCS. Older patients with lipomas in their first two decades have been found in multiple series to harbor more neurological disability than infants and young children. Only a few series distinguish symptomatic from asymptomatic patients and incorporate both operative and observation treatment arms. Tu et al. demonstrated that in a cohort of patients without deficit, those who were observed without surgery showed a 79% rate of progressive neurological decline, whereas those who underwent prophylactic untethering demonstrated a 30% rate of decline at 5 years [14]. Among patients with a fixed deficit, 80% went on to develop a deficit, whereas only 40% of those who had untethering surgery demonstrated decline [14]. Valentini and colleagues reported an operatively treated cohort, 44% of which demonstrated preoperative progressive decline [19].

Despite these widely accepted concepts, it remains likely that multiple factors are involved and that tethering is not the only explanation for the observations. This has been embraced by investigators who advocate the more conservative approach of waiting for convincing clinical signs of decline before intervening operatively [14, 20, 23, 24]. Key observations that support this interpretation and approach include:

1. The development of signs and symptoms is likely to be a matter of emergence and recognition as well as development or progression; examination of the lower extremities and bladder in infants and young children is notably difficult.

2. As more groups have carefully examined young children, it is apparent that the incidence of baseline neurological dysfunction is higher than previously supposed. Neurological dysfunction seems to arise as a result of fundamentally disordered anatomical development in addition to whatever elements of tethering are present.
3. There is clear variation in progression between patients so that it is likely that no single pathophysiological pathway is implicated.
4. Older asymptomatic children who were never treated are also not considered in the analyses of natural history arising from outcome studies of early treated patients. This important omission impedes accurate assessment of the effectiveness of prophylactic surgery.
5. Age could contribute in pathophysiological processes other than tethering as it does in many other body systems.

The more conservative, expectant approach for asymptomatic lipomas resulted in observed decline and need for intervention in only 21% at a mean 5.9 years follow-up of the cohort managed and observed at the Great Ormond Street Hospital for Children in London [23]. By 10 years of follow-up, the cumulative risk of decline was only 40%, which could imply that more than half of prophylactic procedures for asymptomatic lipomas are unnecessary [23]. This is particularly noteworthy because longitudinal studies of cohorts of asymptomatic patients operated on for lipomas have demonstrated late deterioration of function and the development of symptoms over time in significant numbers [9, 21, 23, 34]. This has cast doubt on the effectiveness of prophylactic surgery in conferring long-term protection against neurological decline. When the large series from Paris was reviewed, an actuarial risk of 60% for delayed decline was observed in patients who underwent prophylactic surgical untethering by conventional methods [21]. This contrasts sharply with outcome data published by Pang in a series of consecutive manuscripts that chronologically detailed his cumulative experience with techniques of radical lipoma resection and dural sleeve reconstruction. The progression-free survival observed in 315 patients with these techniques was 88% at 20 years overall and 99% for previously untouched lipomas [8, 25]. However, these techniques have been embraced by few others because of their perceived inherent operative risks and technical demands.

The Way Forward

Surgical Decision-Making

The individual surgeon or clinician must establish his/her preferred approach on the basis of training, experience, technological support, technical capability, and understanding and interpretation of the natural history of these conditions. There is nearly uniform consensus that tethering contributes to decline in patients harboring OSD lesions such that operative untethering is recommended for symptomatic patients. Contemporary surgical and technological adjuncts including the operating microscope

and intraoperative nerve monitoring contribute significantly and are important for reducing risk of iatrogenic injury. Complete untethering and the patulous space between the cord and dura are surgical principles important for interrupting the natural history of the OSD lesions. While untethering operations are generally very safe, careful informed consent should allude to risks of neurological injury, wound-related problems (including possible need for re-operative closure), CSF leaks, infection, bleeding, and loss of effectiveness of the operative procedure over time.

The approach to the asymptomatic patient is more complex. Dermal sinus tracts threaten the patient by both tethering and potential infection so they are uniformly operated upon at diagnosis. Similarly, the role of tethering is widely agreed to impart serious, preventable threat in split cord malformations (SCMs). Further, the site of tethering is focal in SCMs so that most centers appear to support operative untethering before symptoms in the SCMs. For lipomas, more nuance is required in decision-making. Lipoma patients appear to deteriorate with time, but there are variations in the rate and extent of decline, and there is variability in natural history. Furthermore, the role for conventional (limited resection) surgery to prevent decline appears transient in at least some patients. This is inferred from symptomatic patients who have undergone untethering and exhibit recurrence of symptoms after a period of arrest of deterioration.

Conventional surgical untethering arrests decline at least transiently for most patients. The role for more radical resection for asymptomatic patients is more controversial. Pang's large series show that radical resection with reconstruction of the dural sleeve offers the best-reported long-term outcomes with near cure for dorsal and transitional lipomas. The greatest challenge of this work is that sub-total resections of lipomas fared no better or marginally worse than unoperated lipomas over time. The contrast in outcomes between sub-total and radical resections of lipomas is stark.

Despite Pang's claim that the techniques can be learned and perfected by any neurosurgeon, the current literature provides scant evidence that this has occurred so far [8]. Only limited, retrospective, single-institution series from outside of North America have documented outcomes with radical resection [19]. Nonetheless, this work appears to have significantly affected the way in which lipomas are approached in that many surgeons seem increasingly aggressive in reducing the mass of fat present in such lesions and in reconstructing a patulous dural sleeve. The extent to which radical techniques are embraced is a highly personal decision for each surgeon and team that must reflect their training, experience, technological support, and interpretation of the best available techniques.

Future Directions: Investigation and Study Design

The value of retrospective single-institution centers in elucidating the natural history of occult defects is modest. Study design with greater power and scope will be needed to answer these central questions. A multicenter prospective registry, such as the National Spina Bifida Patient Registry (NSBPR) which is supported by the US

Center for Disease Control (CDC), could be an appropriate starting point. Characterization and classification of large numbers of lipomas and their response to treatment could reveal differences that are currently not appreciated. Longitudinal observations of prospectively compiled cohorts over long follow-up times will be required to provide data that will enhance our understanding of the natural history of the tethering lesions. The genetic profile of each lesion must be determined, studied, and recorded. The development of alternate classification schemes that reflect molecular differences between lipomas should be evaluated and encouraged if promising.

Standardized, validated, objective metrics of outcome are also needed. At present, all available outcome parameters for evaluating tethered cord and neurological function are subjective. There is no disease-specific validated outcome measurement for dysraphism. The ultimate objective would be standardized, validated measures that are not performed by the treating team. Only when large cohorts of patients with OSD lesions are followed longitudinally with the best available metrics will the true natural history of the OSD conditions be known with certainty.

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Cutaneous Stigmata and the Occult Spinal Dysraphisms

4

Jaspreet Johal, Charlotte Wilson, R. Shane Tubbs, and W. Jerry Oakes

Introduction

The term occult spinal dysraphism (OSD) refers to a wide range of spinal abnormalities that manifest with congenital absence of varying portions of the dorsal elements of the spine. Conditions that fall under the category of OSD include tethered cord syndrome, lipomeningomyelocele, neurenteric cysts, and dermal sinus tracts [1]. These abnormalities act to attach the spine improperly to surrounding structures such as dura mater, bone, and soft tissues [2]. Such abnormal attachment can result in tethered cord symptoms. The actual incidence of spinal dysraphisms is difficult to ascertain as they can be occult and it is not plausible to screen all neonates for them [3]. This category of anomalies often presents with concurrent skin lesions that include, but are not limited to, subcutaneous lipomas, atretic meningoceles, dermal sinuses, hemangiomas, focal hypertrichosis, and the presence of a

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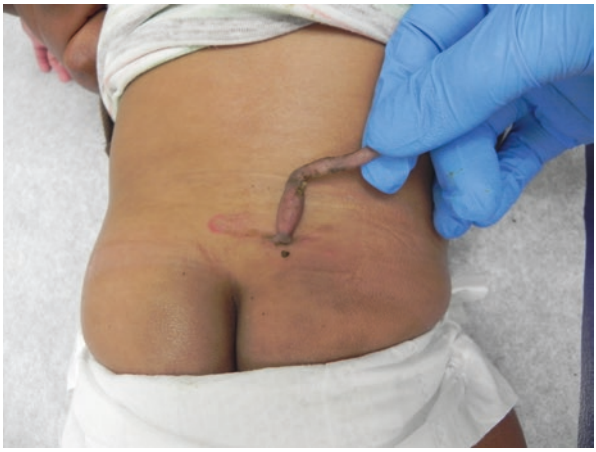

Fig. 4.1 The so-called human tail or dorsal appendage

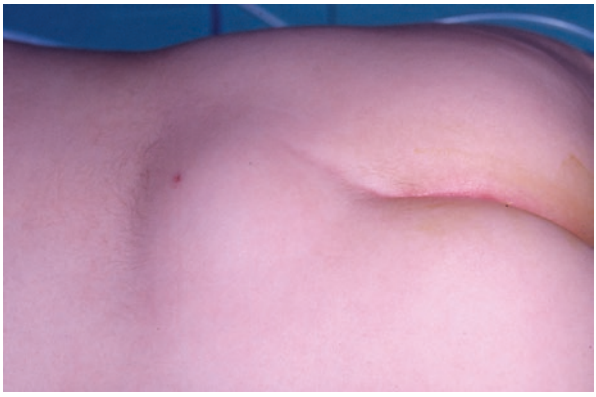

Fig. 4.2 Subcutaneous lipoma

human tail (Figs. 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 4.10, and 4.11) [4]. It has been suggested that all neonates presenting with suspicious cutaneous lesions be investigated for a potential OSD, especially when found over the midline lumbosacral region. Imaging modalities that can be used to examine for OSD include lumbar sonography, MRI, and CT of the appropriate area with subsequent neurosurgical intervention to limit potential permanent injury [2, 3, 5–7] .

A recent analysis by Schropp and colleagues [8] revealed that up to 86% of cases of OSD are associated with cutaneous lesions; however, surgical case series and reports seldom focus on which cutaneous lesion is associated with a particular spinal anomaly [8]. Nonetheless, Schropp et al. performed a correlation analysis and concluded that among the most commonly associated cutaneous stigmata were subcutaneous lipomas, vascular nevi, and skin dimples. Specific associations between cutaneous lesions and spinal anomalies were also reported. Subcutaneous lipomas in particular were found to indicate an underlying spinal lipoma or lipomyelomeningocele. Spinal lipomas were also associated with stigmata such as vascular nevi and

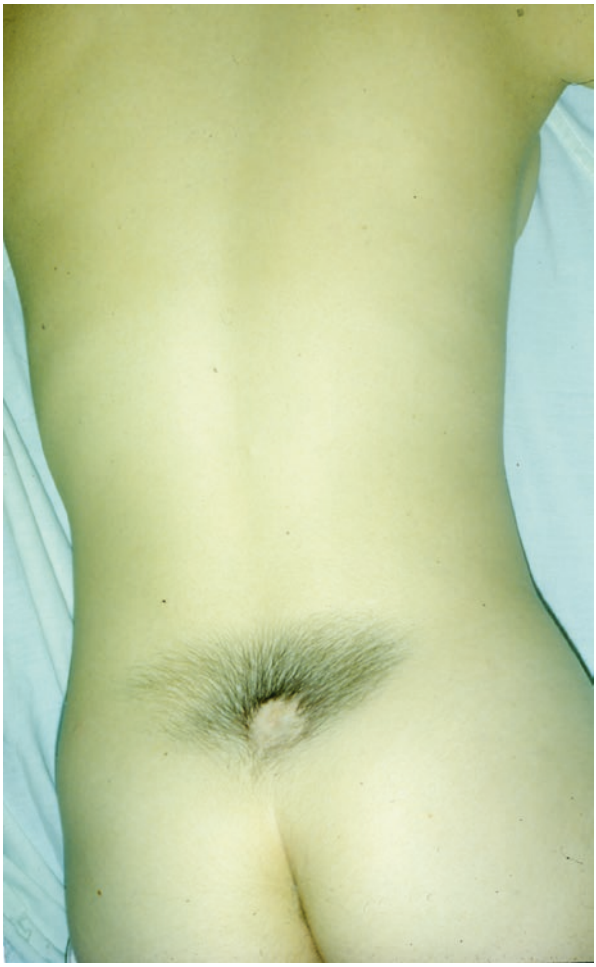

Fig. 4.3 Focal hirsutism

skin tags [8]. Schropp and colleagues [8] also reported associations between certain cutaneous lesions. For instance, they found that dermal sinuses are more likely to be correlated with vascular nevi and hypertrichosis [8].The aim of the present review is to summarize the various cutaneous stigmata associated with the occurrence of OSD.

Hemangiomas and Vascular Nevi

Most vascular stigmata in the neonate are insignificant findings warranting no further investigation, and this is particularly true of lesions on the back [9, 10]. Among the broad range of vascular stigmata seen in the pediatric population, vascular nevi and hemangiomas are most commonly associated with OSD and other spinal

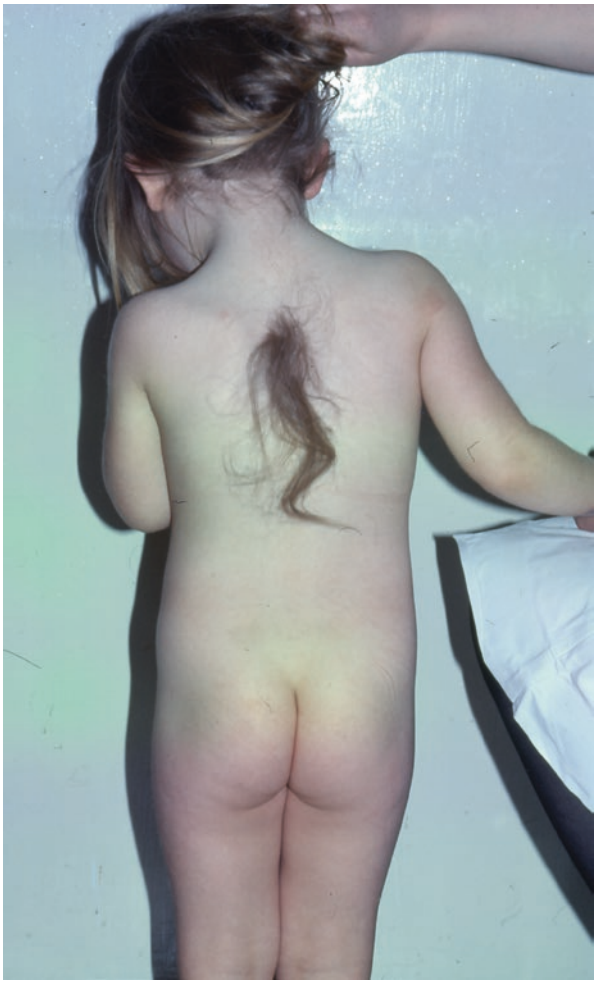

Fig. 4.4 Focal hirsutism of the thorax

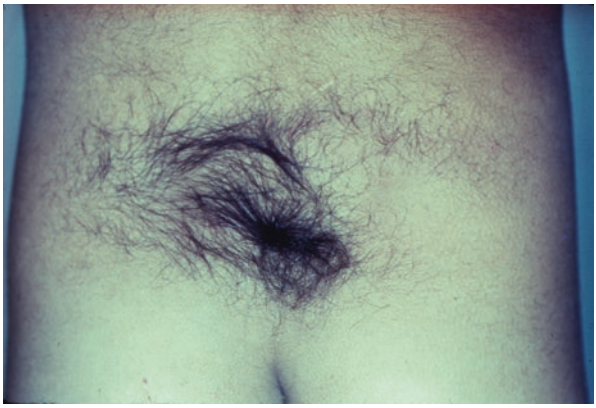

Fig. 4.5 More diffuse hypertrichosis associated with OSD

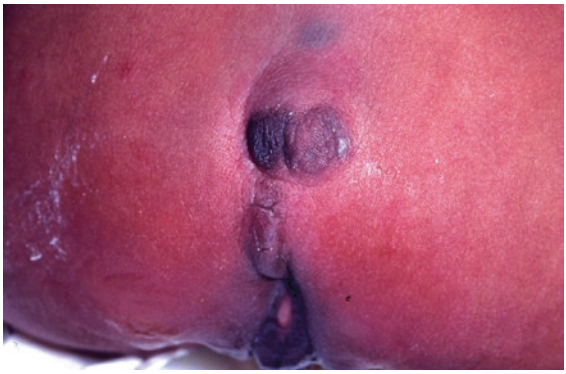

Fig. 4.6 Atretic meningocele

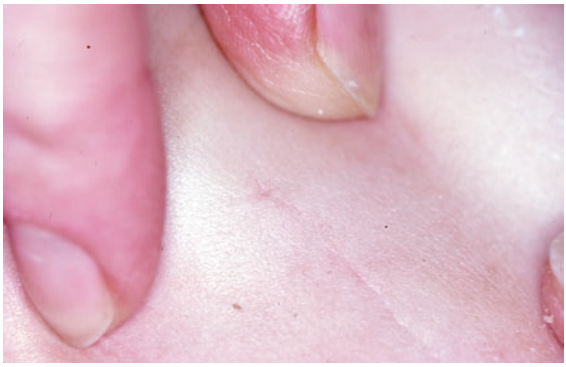

Fig. 4.7 Small dermal sinus

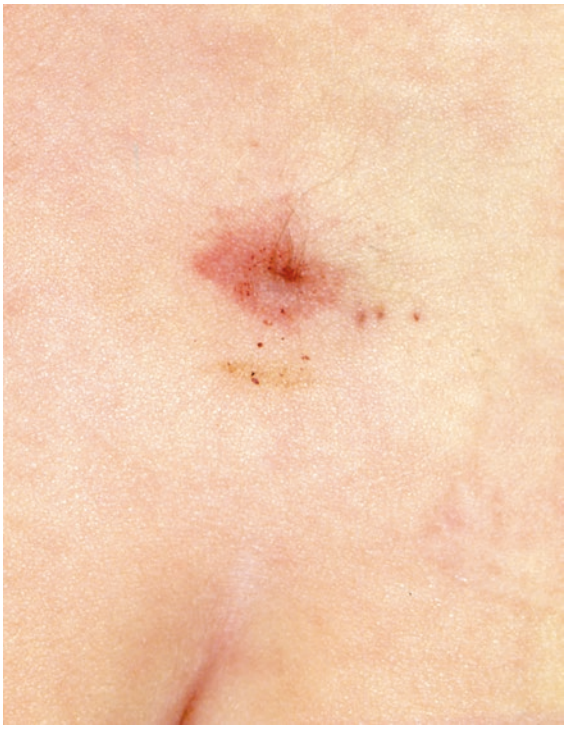

Fig. 4.8 Capillary hemangioma

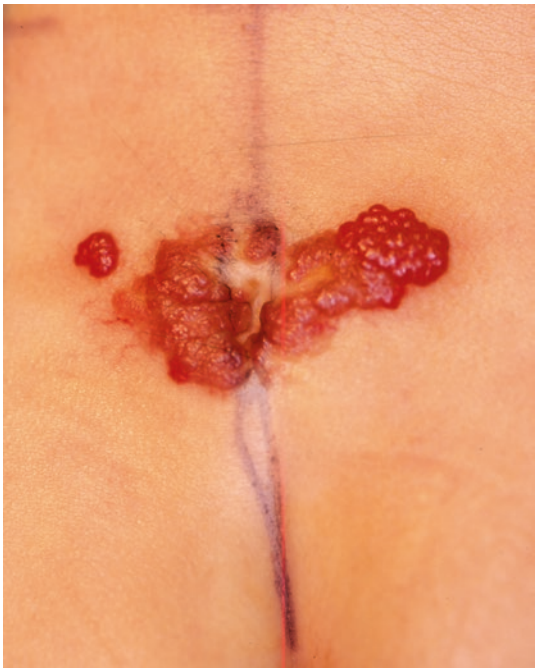

Fig. 4.9 Capillary hemangioma

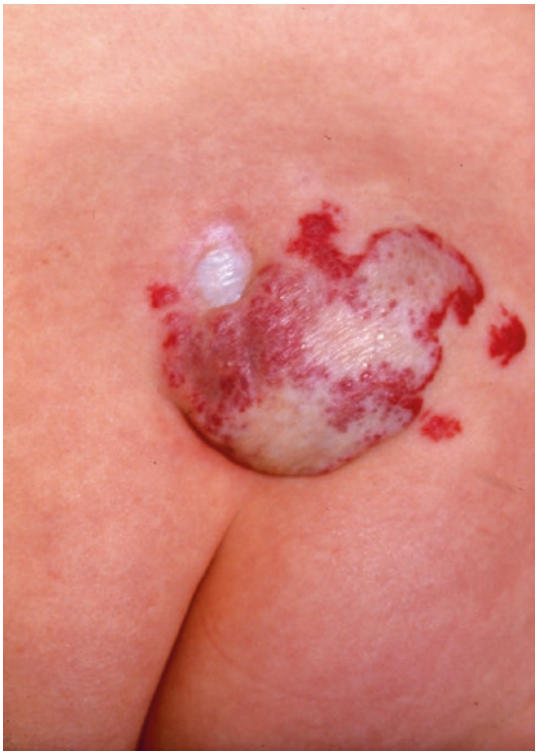

Fig. 4.10 Capillary hemangioma

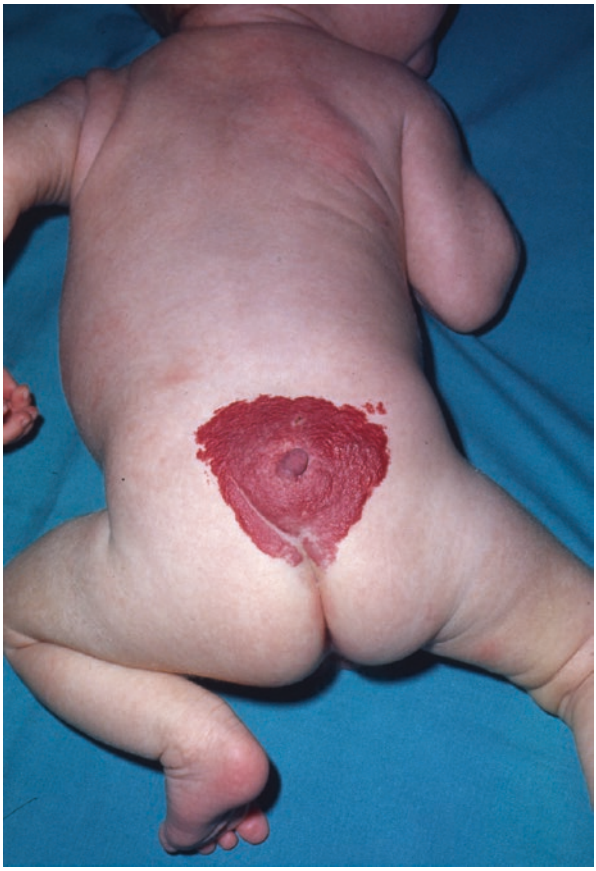

Fig. 4.11 Capillary hemangioma

anomalies [8]. Some authors consider hemangioma to be a distinct cutaneous lesion, while others regard it as a subcategory of vascular nevi [11]. According to Senthilkumar and Thappa [11], vascular nevi encompass hemangiomas, angiokeratomas, and vascular malformations. Hemangiomas are distinguished from vascular malformations, in which there is no endothelial cell proliferation [11]. The terms "salmon patch" and "stork bite" are also used clinically to describe lesions that are considered vascular nevi [8].

Hemangiomas in the infant population, described as the most common benign tumors of childhood, are vascular tumors resulting from excessive endothelial growth [11]. Rarely, they can become complicated by thrombosis, trauma, or sepsis, but they usually follow a course of slow involution and can regress completely on their own [11–13]. A small percentage of hemangiomas have associated congenital anomalies [11]. Hemangiomas located in the midline lumbosacral region are believed by some authors to indicate an underlying OSD [8, 14–16]. Other lesions falling under the category of vascular nevi have also been associated with OSD. In addition, vascular nevi are reported to correlate with dermal sinuses and spinal lipomas [8].

Hypertrichosis and Focal Hirsutism

Abnormal hair growth among the pediatric population can occur as diffuse hypertrichosis that affects the entire body or as more focal patches [8, 17]. Hypertrichosis can be further categorized on the basis of age of onset (as congenital or acquired), pattern of distribution, site(s) involved, and whether it is an isolated anomaly or is associated with other abnormalities [17]. Acquired hypertrichosis is more common than the congenital form, but congenital hypertrichosis is associated with OSD and other spinal anomalies [17]. It has been established that anomalies such as OSD are more commonly associated with focal hairy patches than diffuse

hypertrichosis [8, 18]. Tubbs and colleagues [19] found that 37% of cases of meningocele manqué studied were associated with focal hirsutism. Within their study, meningoceles manqués were defined as abnormal, dorsally located bands tethering the spinal cord to surrounding tissues [19, 20]. A focal hairy match can also occur alongside other lesions such as dimples, or skin pits can be associated with OSD, which warrants further investigation [21]. Localized hypertrichosis associated with OSD often occurs in the lumbosacral region and is V-shaped and poorly circumscribed [22]. Diffuse hypertrichosis, in contrast, is not associated with any specific spinal anomaly but is correlated with the presence of dermal sinuses [8].

Subcutaneous Lipomas

Subcutaneous lipoma occurs as a localized excess of mature fat cells and is regarded as an indicator of spinal lipoma or lipomyelomeningocele [8]. It can occasionally present by causing spontaneous neurological deterioration secondary to tethering of the cord, filum, or nerve roots [23]. Lipomas can be located in the dermis or spinal canal and can extend from the dermis to the intraspinal space via a concurrent vertebral defect [22]. Intraspinal lipomas can broadly be categorized as occurring in association with either the filum or the conus. Those associated with the filum have very limited morbidity and can benefit in both the short and long term from surgical intervention. Lipomas associated with the conus are much more structurally complex, are correlated with more severe deficits and defects, and can entail significant surgical risks [23, 24]. Subcutaneous lipomas have also been associated with other cutaneous stigmata, namely, skin tags, vascular nevi, and deviations of the gluteal fold [8].

Dermal Sinuses

Dermal sinuses are congenital cutaneous lesions located along embryonic fusion lines. Although they are congenital in formation, they are not always noticed until later in childhood, when they begin to enlarge. They are located on the face, scalp, and along the spinal axis [22]. Dermal sinuses in the midline or nasal region should be more closely monitored as they often have an intracranial connection [22, 25].

Dermal sinuses often have small tracts that connect a dermal cyst to the surface of the skin. Multiple analyses of OSD and isolated dermal sinuses have shown a relationship between this anomaly and dermal tracts [8, 18, 22]. Dermal sinuses also occur with a variety of other cutaneous lesions that are correlated with spinal dysraphism, including pseudotails, vascular nevi, and hypertrichosis [8, 26].

Human Tails

Human tails are rare occurrences that can be classified on the basis of their tissue composition as either true tails or pseudotails [27]. They can show some degree of association with OSD and other spinal anomalies as they are located in the lumbosacral region and can be connected to some spinal structures [8, 18, 22, 27]. Acrochordon, another cutaneous lesion somewhat similar in structure, can also be associated with spinal dysraphism [22]. Acrochordons are small, skin-covered papules or nodules, either sessile or pedunculated. They comprise of epidermis and a dermal stalk [22]. A true human tail is distinguished from other similar anomalies by its central core of adipose tissue, a localized vasculature, and bundles of associated nerve and muscle fibers [22]. Pseudotails can be defined as stump-like structures that functionally exist as hamartomas made of adipose tissue and cartilage [22]. Pseudotails are also incapable of movement, while true human tails can display some degree of mobility [27]. Human tails can broadly be categorized as those involving only embryonic soft tissue, those arising from exaggerated growth of the existing and unfused coccygeal vertebrae, and those containing additional vertebrae [27, 28]. Human tails can occur alongside other implicated cutaneous stigmata such as vascular nevi and cutaneous dimples or pits [8].

Other Lesions

Cutaneous stigmata other than those previously described can also be associated with spinal dysraphism, although they are usually benign clinical findings. Dimples in the lumbosacral region are common but can occasionally be associated with OSD [18, 22]. Most dimples and similar skins lesions are benign and do not warrant extensive investigation, especially sacral lesions within the gluteal crease. Dimples that may indicate an underlying deformity are deep, larger than 0.5 cm, located within the superior portion of the gluteal crease or above it, and associated with other types of suspicious lesions [22]. Lesions initially thought to be deep dimples can prove to be dermal sinuses that directly communicate with the spinal cord [22]. Individuals with dimples associated with spinal dysraphism also commonly display other concurrent cutaneous lesions, making it difficult to relate this lesion to OSD [8]. Abnormal retractions of the skin can occur as either atypical dimples or pori. If there is associated spinal dysraphism, these pori are the superficial openings of dermal sinuses [8]. Aplasia cutis is another cutaneous lesion rarely associated with spinal dysraphism which is described as congenital absence of skin, dermal

appendages, and in some instances the subcutaneous tissue [29]. This anomaly is most common on the scalp and head but can also occur at other sites [22]. Rarely, aplasia cutis has been reported in the lumbosacral region and correlated with spinal dysraphism [22, 30].

Conclusion

A broad range of cutaneous stigmata have some degree of association with spinal dysraphism. This range includes, but is not limited to, hypertrichosis, subcutaneous lipomas, dermal sinuses, hemangiomas and other vascular abnormalities, and the phenomenon of human tails. Although many of these lesions are often benign, they warrant further investigation as they can indicate hidden anomalies such as spinal dysraphism. Investigation with imaging techniques such as ultrasonography, CT, and MRI is recommended for suspicious lesions, especially when different subtypes of cutaneous stigmata are observed in the same individual. Areas of further study include increased reporting of cases where different types of cutaneous stigmata are seen in a patient with spinal dysraphism. Further research should also focus on establishing diagnostic criteria for a clinical syndrome that relates various clinical stigmata to spinal dysraphism. This would go beyond merely reporting associations between cutaneous lesions and OSD.

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The Filum Terminale

5

Erfanul Saker, Charlotte Wilson, and R. Shane Tubbs

History

The filum terminale was known in antiquity (Figs. 5.1 and 5.2) to many including Galen, Rhazes, Haly Abbas, and Avicenna. It has been termed the unpaired nerve, *ligamentum pia matis*, *nervus impar sacrus*, *le nerf impair*, *le nerve unique*, *nervum sine conjuge*, and *nervum conjuge carentem*. These latter two terms refer to a nerve without a companion. Galen made special note of this structure in animals in his *De Ossibus ad Tirones* (*On Bones for Beginners*). He described the filum as "What remains of the spinal cord at the end of the third bone [of the coccyx] emerges alone and unpaired." Vesalius illustrated the filum terminale or at least its external component on plate 52 of his *De Humani Corporis Fabrica* of 1543 (Fig. 5.3). Many early studies, however, have described the filum terminale simply as a fibrovascular band attachment of the spinal cord to the coccyx [1–4]. Therefore, little attention was given to study this structure until the beginning of the twelfth century [2].

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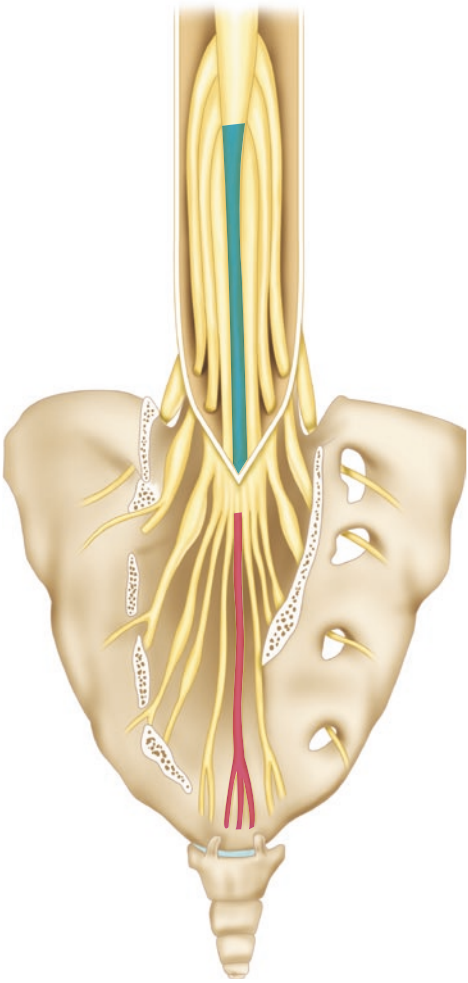

Fig. 5.1 Schematic drawing of the filum terminale internum (green) and externum (red)

The Filum Terminale and Tethered Spinal Cord

As early as 1910, Fuchs [5] hypothesized that intermittent incontinence seen in myelomeningocele patients during spinal flexion was due to stretch-induced abnormal tension on the distal spinal cord [6, 7]. Later, Kunitomo [8] in 1918 and Streeter [9] in 1919 focused their studies on the embryology of the conus medullaris and filum terminale in humans, eventually enhancing the understanding of the concept of a "tethered spinal cord" [1, 7].

In 1940, Lichtenstein [10] introduced the idea of symptomatology due to tethering-induced spinal cord lesions and employed the term "spinal dysraphism" [7, 11]. A few years later, he wrote about distant neuroanatomic defects in cases of spina bifida and believed the findings were dependent on fixation of

Fig. 5.2 Plate 52 (redrawn) from *De Humani Corporis Fabrica* (1543) illustrating the filum terminale

the spinal cord at an abnormally low level with abnormal stretching of the cord [11, 12] (Fig. 5.2). In a paper by Parker and McConnell [13], Riley suggested that a shortened filum terminale might be the basic cause [11]. Bassett [14] in 1950 and Rogers et al. [15] in 1971 reported the cases of neurological signs and symptoms observed in patients with an elongated spinal cord attached to a sacral lipoma. However, both attributed the neurological signs to a congenital nature [7].

It was not until 1953 when Garceau [16], with contributions from Heimberger, first attributed neurological sequelae to a taut filum terminale [4]. He hypothesized that stretching of the spinal cord caused spinal cord dysfunction [6, 7]. Garceau described three patients who demonstrated improvement of progressive spastic paralysis following exploratory lumbar laminectomy and severance of a thick, tight

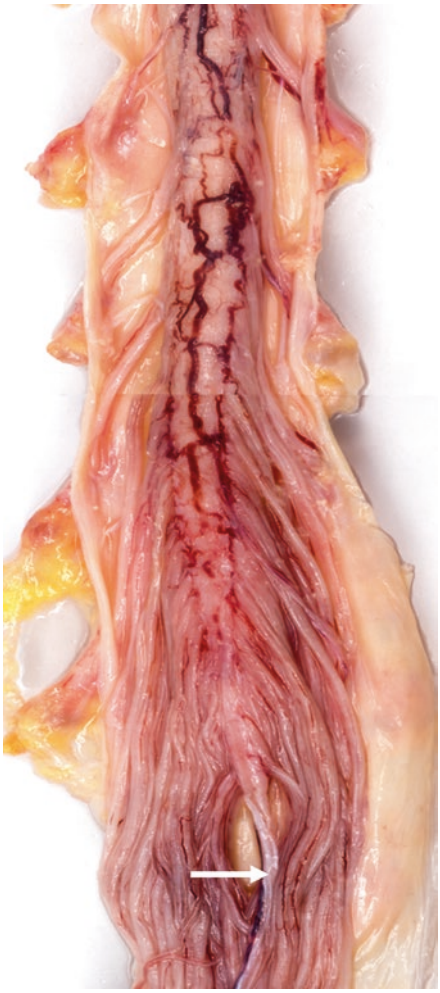

Fig. 5.3 Cadaveric view of the filum terminale internum (arrow)

filum terminale [11, 16]. In the following years, the importance of a tight filum terminale when explaining stretch-induced symptomatology was supported by Jones and Love [11] and James [17] and Lassman [7].

Embryology

The embryonic development of the central nervous system (CNS) involves three major steps: neurulation, canalization of the tail bud, and dedifferentiation [18]. During the fourth week of development, in the region of the fourth to sixth pair of somites, primary neurulation begins [19]. Initially, the ectoderm overlying the notochord proliferates to form the neural plate, which later involutes to form the

neural folds and eventually closes to form the neural tube [20, 21]. At this stage the neural plate and neural tube, which begins to close by day 22–23, are split into a cranial and caudal portion with the caudal one-third representing the future spinal cord [19].

Following primary neurulation, the distal neural tube undergoes canalization, a process that involves vacuolization, canal formation by joining of vacuoles, and programmed cell death (apoptosis) [18, 20]. Secondary neurulation begins around the 27th day and starts below the level of somites 32–34, which correspond to the future third through fifth sacral vertebra [3]. This involves tissue located within the caudal cell mass (the remnant of Hensen's node) distal to the posterior neuropore [6, 17, 22]. The distal neural tube forms from fused vacuoles that developed from the caudal cell mass, which were formed by the undifferentiated cells of the primitive streak. At day 52 of development, caudal neural tube regresses and develops into the spinal cord caudal to S2, including the conus medullaris, cauda equina, and the future filum terminale [2, 6, 20, 22, 23]. During the end of the canalization period, the ventriculus terminalis forms at the terminal end of the neural tube near the coccyx, which is the site of the future conus medullaris [20]. Errors in the process of canalization of the tail bud cause congenital malformations such as a thick filum terminale, filar lipoma, and terminal myelocystocele [18].

In early embryonic life, the spinal cord occupies the entire length of the vertebral canal [24]. Kunitomo [8] published a careful study of the tail region in a large number of human embryos demonstrating that in very young specimens, the spinal cord reaches the extreme tip of the tail and throughout its length is quite uniform in structure [9, 23, 25]. When it reaches the 11–15 mm stage, the cord can be divided at about the level of the 32nd vertebra into two parts—a cranial region, having a wide central canal, and a slender caudal section, having a narrow canal with walls consisting only of an ependymal zone [8, 9, 23, 25]. The region of the spinal cord caudal to the 30th segment undergoes dedifferentiation (tissue reverting to an earlier embryonic type, with subsequent redifferentiation), while the more cephalic part of it persists as the ventriculus terminalis [23, 25, 26].

Secondary neurulation proceeds with the more caudal end, which is adherent to the overlying ectoderm, regressing and undergoing retrogressive differentiation (complete regression and disappearance of caudal tail by apoptosis) [24]. This caudal atrophic portion, with the walls of the intermediate part of the terminal ventricle and its covering pia mater, eventually forms the delicate filum terminale. The separated portion of the terminal ventricle briefly persists, but it usually disappears before birth [8, 24, 27].

When the embryo reaches 30 mm in length, around the second trimester, there is an increasing discrepancy between the anatomical level of the vertebral column and the spinal cord, the former elongating more rapidly than the latter [23–25]. This results in a relative displacement of the vertebral column and spinal canal with the ventriculus terminalis lying about nine segments higher than its original position by the 25th week [24]. By the time the adult form is attained, two more segments will have been added contributing to the disproportion [23]. Proceeding

caudally, the nerve roots lengthen and become progressively more oblique. By full term, near 40 weeks, the conus medullaris lies between the first and third lumbar vertebrae [24].

Kunitomo pointed out that this disproportion in growth and the dedifferentiation of the caudal end of the medullary were two factors involved in the formation of the filum terminale [8, 25]. Streeter [9] evaluated these factors and its role in the formation of the filum terminale by determining the elongation of the nerve roots [25]. Streeter concluded that the filum terminale, similar to the sacral nerve roots, "elongates by interstitial growth in adaptation to the ascending displacement of the spinal cord, rather than as a result of a simple stretching" [9, 25].

Anatomy

The spinal cord occupies the superior two-thirds of the vertebral canal and terminates caudally as the conus medullaris. The length of the conus medullaris and filum terminale is directly proportional to the body length, although minor variations exist among subjects of the same height [25]. The fourth sacral segment marks the beginning of the conus medullaris, based on observations that the cells innervating the muscles of the lower limb disappear at this level [25]. In the later stages of fetal life, the conus medullaris lies between L3 and S5. In premature and term neonates, it lies between L1 and L3, and in children between 1 and 7 years of age, it lies between T12 and L3. In the adult, the spinal cord terminates on average at the level of the middle third body of L1. Sometimes, it may end as high as the middle third body of T11 or as low as the middle third body of L3. Its position rises marginally in vertebral flexion, and there is some correlation with the length of the trunk, especially in females [24].

Filum Terminale Internum

The entire filum terminale extends approximately 20 cm long and descends from the apex of the conus medullaris within the lumbar cistern to the dorsum of the coccyx, where it blends into the connective tissue covering this bone [24, 28]. It consists of glial and ependymal cells and was divided by Luschka into two components: an upper intradural component (filum terminale internum) (Fig. 5.3) and lower extradural component (filum terminale externum) [2, 4, 29] (Fig. 5.1). The filum terminale internum (FTI) measures about 15 cm [24, 30] in length and is continued within extensions of the dura and arachnoid mater. Psammoma bodies were found at the junction between the two parts of the dura, mainly in older subjects [25, 31]. De Vloo et al. [32] performed a human cadaveric study and found the FTI was about 16 cm long and oblate cone-shaped with its tip pointing caudally. An ample part of the subarachnoid space surrounds the filum terminale internum and is the site of access to the cerebrospinal fluid (CSF) via a lumbar puncture [24].

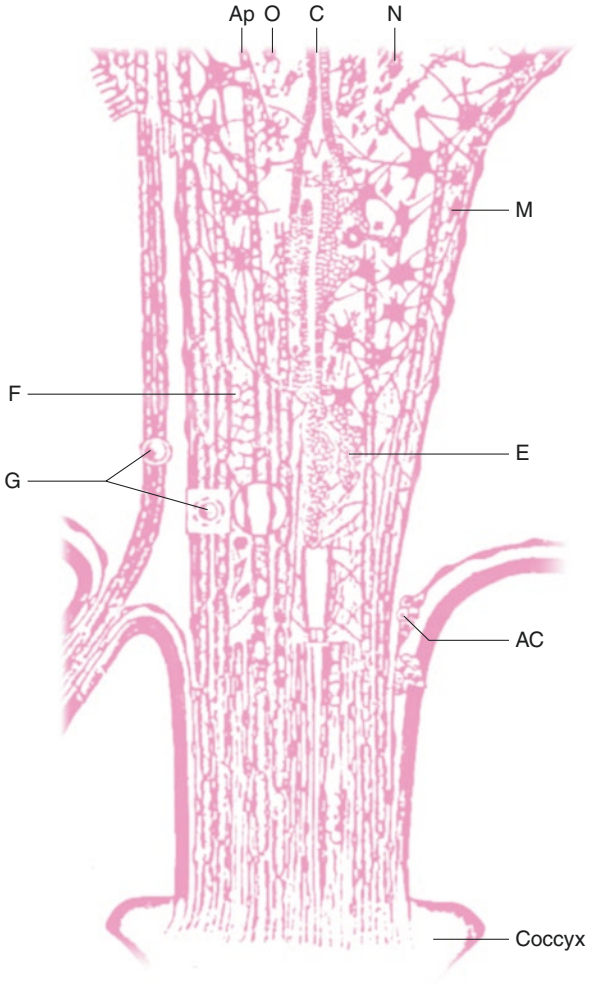

Fig. 5.4 Illustration of the microanatomy of the filum terminale (after Tarlov [25]). Various structures shown include the following: interfascicular oligodendrocytes (O), protoplasmic astrocyte (Ap), central canal (C), terminal ventricle (V), nerve cells (N), microglia cells (M), ganglion cells (G), ependymal cells (E), and fat cells (F)

In 1933, Harmeier [33] described the microscopic anatomy of the filum terminale internum. Large collections of ependymal cells, neuroblasts, and corpora amylacea were found scattered throughout the filum and within the tissue. At the periphery, ganglion cells were also found. Abundant myelin was noted in the proximal half of the filum with axons extending all the way down [2]. Tarlov [25] added a more detailed description of the FTI (Fig. 5.4). He observed that at the transition between the conus medullaris and the filum terminale, the difference between anterior and posterior horns became gradually less pronounced with lack of demarcation of the gray and white matter [2]. Large numbers of glial cells, similar to those found in the central nervous system, were noted within the intradural portion of the filum. These glial cells consisted of ependymal cells, astrocytes, oligodendrocytes, and microglial cells and at times constituted the main component of the filum (Fig. 5.4).

Choi et al. [1] emphasized the fact that the plethora of glial cells in the conus medullaris and filum terminale is a feature characteristic of the normal filum and that it should not be confused with the presence of a true neoplasm in this region. Tarlov also observed that the ependymal cells were the most abundant and the last to disappear of all the interstitial cells, as it extends as far as the first 2 cm of the extradural part of the filum (FTE) [2, 25]. These ependymal cells were thought to be the origin of ependymomas (myxopapillary ependymomas) arising at the level of the cauda equine [4].

Filum Terminale Externum

The lower part, or filum terminale externum (FTE), also called the coccygeal ligament [2, 4, 28], measures about 5 cm in length and is adherent to the dura mater. It descends from the apex of the tubular sheath and connects the distal dural cul-de-sac with the periosteum of the coccyx [24, 30, 32]. Various investigators have studied the length of the FTE. Tarlov found the FTE to measure approximately 2.2 cm in the newborn infant. In adults, he found that the mean length was 7.5 cm [4, 25]. In their cadaveric study, De Vloo observed the FTE to be approximately 7 cm long and hourglass shaped [32]. Others have found that the mean length of the FTE is approximately 8 cm. Tubbs et al. [4] examined 15 adult cadavers and found the length of the FTE measured in length from 7 to 10.5 cm (mean 8 cm), which contradicted comments made by Bale [34] that after birth the FTE is difficult to find.

The filum terminale reaches as far as the caudal border of the second sacral vertebra. The sacral canal also contains the cauda equine and the spinal meninges. At the level opposite to the middle of the sacrum (S2), the lower sacral spinal roots and filum terminale pierce the arachnoid and dura mater [28]. The filum terminale, with its meningeal coverings, emerges below the sacral hiatus and passes downward across the dorsal surface of S5 and the sacrococcygeal joint to reach the coccyx, with the first coccygeal nerve running along the filum [24, 25]. The filum is also surrounded by the nerves forming the cauda equina, from which it can be characteristically recognized by its bluish-white hue [30].

The filum is encircled by a glistening connective tissue sheath and is continuous with the pia mater at higher levels. The denticulate ligament, which extends as a narrow band along the lateral aspect of the pia mater, becomes continuous with the sheath of the filum [25]. Sometimes, a few strands of nerve fibers adhere to its upper outer surface, which possibly represent the roots of rudimentary second and third coccygeal nerves [25, 30, 32]. Further, the first 5–6 mm of the filum includes a central canal [28]. De Vloo first documented histologically that the dural sac and FTI fuse together into the FTE. Additionally, by performing the first human filum terminale stain, De Vloo observed that the filum terminale, along with the dentate ligaments, has the capability of protecting the spinal cord against physiologic stress [32].

Variations

Knowing the vertebral level in which the majority of spinal cords terminate and being aware that the sites of conus termination vary among individuals is important [28]. For example, deficits seen in patients who have experienced neurologic injuries from fractures, especially vertebral burst fractures, and osteoporotic vertebral collapse at the thoracolumbar junction (T12 and L1) differ depending on the location of the conus. Knowing the variations in the conus position also has practical implications when performing invasive procedure such as a lumbar puncture (spinal tap) or when performing myelography [28, 35]. Myelography allows a dynamic assessment to be made of the spinal canal dimension between flexion and extension, which makes it a valuable tool in the investigation of spinal stenosis [35].

Barson [36] found the level of the conus medullaris is altered slightly by the degree of flexion of the spine. It is feasible that the position of the conus may vary considerably in the erect position and between flexion and extension. This may be of clinical relevance as physicians may find it advantageous to place patients in such positions for better access of the cerebrospinal fluid when performing a lumbar puncture [35].

Saifuddin et al. [35] in a study, with 504 adult cases without spinal deformity, found that the average conus position was at the lower third of the L1 body, with a range from the middle third of T12 to the upper third of L3. They found that the conus position was slightly lower in males than in females. Similar results were obtained by Rostamzadeh et al. [37] except their study did not show a significant difference between conus position among genders. Warder and Oakes [38] described 73 patients with the tethered cord syndrome and found the conus terminated at or above the L1–L2 disc space. Likewise, Pinto et al.'s [39] cadaveric study demonstrated the inferior tip of the conus medullaris at or above the L2 level. Two of their cadavers demonstrated the inferior tip of the conus medullaris at the level of the L2–L3 disc space and did not have clinical histories of tethered cord syndrome. In addition, those cadavers did not exhibit filum terminale thicknesses of more than 2 mm at the initial point or at the midpoint [39].

The vast majority of the filum fuses on the dorsal midline of the dura, with some fusing to the left or right of the midline. The level of fusion varies anywhere from the lower L5 vertebral body to the upper S3 body. The majority of fila fuse at or below S1, while a small sample fuse above the S1 level. Forty-four percent of the time the fusion is at the same level as the termination of the dural sac [28, 39, 40]. Pinto et al.'s study demonstrated that the most frequent fusion level was S2; however, 12 cadavers demonstrated a filum that fused above S2 [39]. The importance of these findings has surgical implications as a S1 laminectomy is often used to section the filum terminale in patients with TCS. The variation in the level and fusion of the conus and filum should be taken into consideration before surgery or a procedure is performed [39].

Pathology

Tethered Cord Syndrome

The filum terminale has clinical significance in its contribution to tethered cord syndrome (TCS), a form of occult spinal dysraphism. TCS refers to a collection of signs and symptoms of motor and sensory neuron dysfunction attributable to spinal cord traction [6, 39]. Classically, this syndrome is associated with an abnormally low conus medullaris (below the L2 vertebral level) and in some patients a thickened filum terminale [18]. Although a tight filum terminale is present at birth, late onset of symptoms can be explained by the cumulative effect of hypoxia on the conus medullaris. According to Yamada et al. [41], clinical symptoms appear after accumulation of hypoxic damage in the neural tissue [18]. More recently, TCS has been broadened to include patients with "tethering or anchoring" of the cervical or thoracic cord, as well as those with presumed increased tension on the lower cord despite normal-level conus medullaris [6]. TCS has been associated with a number of disorders including the vast spectrum of spinal dysraphism (i.e., scoliosis), trauma, infection, and neoplasm [6, 39].

TCS can be seen in children; onset of symptoms is often between 5 and 15 years [39]. In children, an abnormal filum terminale (Figs. 5.5 and 5.6) could be responsible for the syndrome as a possible consequence of a congenital error in the canalization of the caudal bud of the spinal cord. This error would cause adhesion of the filum to adjacent structures, preventing it from ascending within the vertebral canal [28, 39]. However, TCS can also occur in adults. In this case a subclinical degree of spinal cord traction is present. The traction can become clinically apparent when abrupt cord traction occurs because of sudden flexion of the vertebral canal (e.g., the abdominal flexion movements and trauma resulting from MVA) [28, 39].

Symptoms of TCS include weakness of the lower extremities and gait disturbances [42]. The pattern of weakness does not necessarily correspond to cord injury at a certain level nor does sensory deficits follow an exact dermatomal pattern, so

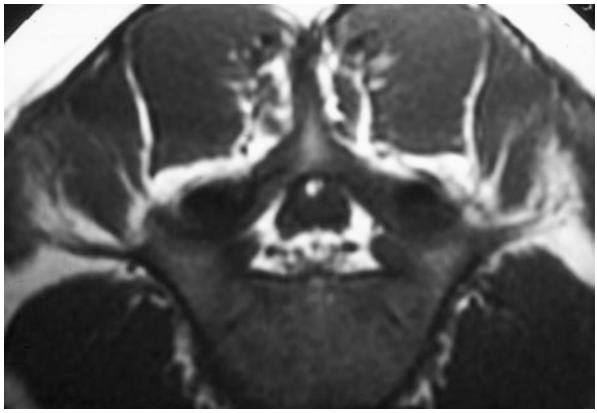

Fig. 5.5 Axial T1-weighted MRI noting a centrally placed fatty infiltrated filum terminale

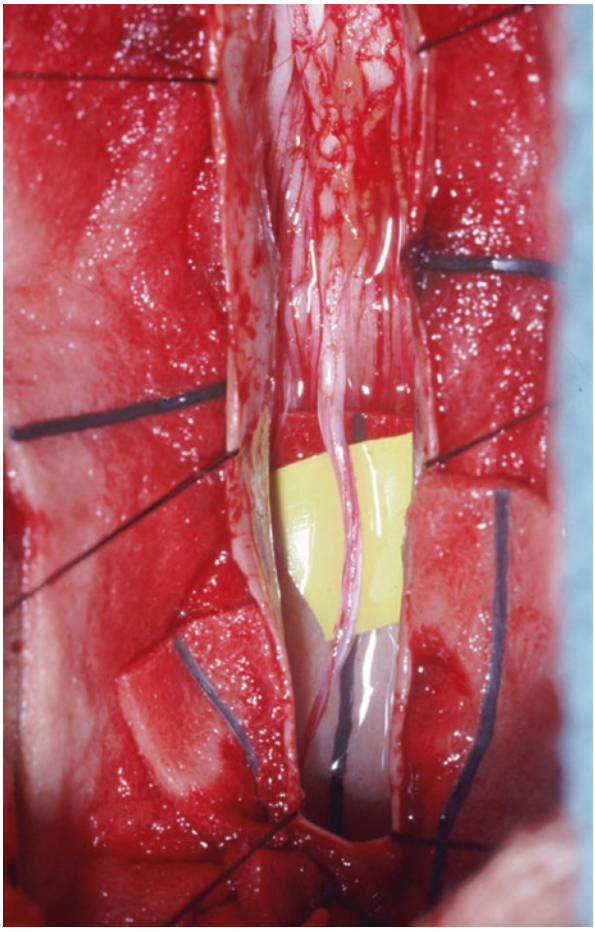

Fig. 5.6 Surgical exposure of a fatty infiltrated filum terminale (over yellow paper)

that an L5 deficit could be combined with one at L2 [42]. The most common neurologic deficit is pain in the lower back and pain radiating into the lower limbs. Patients may also exhibit other symptoms such as cavovarus foot, length differences between the lower limbs, cutaneous alterations in the lumbar and sacral regions (lipomas, hypertrichosis, hemangiomas, and skin dimples), and sphincter control deficiencies [39].

Fatty Infiltration

Incidental fat within the filum terminale is found in up to 17% of normal adults, frequently seen on routine magnetic resonance imaging (MRI) of the lumbosacral spine [2, 43] (Fig. 5.7). With infiltration of adipose tissue, the filum terminale

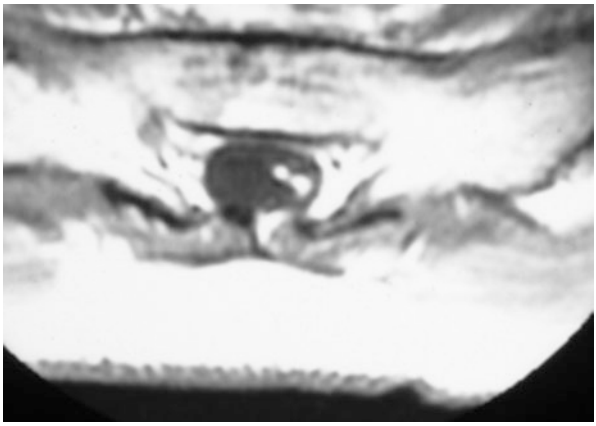

Fig. 5.7 Axial T1-weighted MRI noting duplicated and fatty infiltrated fila terminale

thickens, loses its flexibility, and shortens, which can provoke tethered cord syndrome, and is often seen in patients with spina bifida occulta [28, 43, 44] (Fig. 5.5). It was theorized that the stretching of the cauda equina resultant of tension from the infiltrates leads to impaired mitochondrial oxidative metabolism and subsequent neuronal dysfunction at the lumbosacral level [41]. Such stretching of the lower spinal cord results in low back pain accompanied by a variety of motor and sensory signs and symptoms in the lower extremities [28]. McLendon et al. [43] described a case of a patient who presented with low back pain but no spina bifida occulta but was nonetheless found to have adipose tissue in the filum on unenhanced computed tomographic (CT) scan. Subsequently, the patient was found to have a tethered cord [43].

McLendon et al. [43] also reviewed the occurrence of fatty tissue in the fila from 12 patients with the tethered cord syndrome and in the fila from 47 neurologically asymptomatic patients. The results obtained suggested that adipose tissue may be found in the filum terminale in up to 19% of the asymptomatic adult population, but only 6% of the masses were large enough for CT detection. The finding of fat is not diagnostic for tethering of the spinal cord but, when fat is seen on the CT scan, the possibility of tethering of the spinal cord must be raised. Contrast-enhanced CT myelographic studies or magnetic resonance imaging of the lumbar region is indicated to rule out caudal displacement of the conus medullaris, indicative of tethering [34]. MRI shows the conus medullaris extending further inferiorly than normal with infiltration of adipose tissue into the filum terminale [28].

Duplicated Filum Terminale

Split cord malformation (SCM) is a rare subset of neural tube defects whereby the spinal cord bifurcates longitudinally by a fibrous or bony spur. Pang et al. [45] believed SCM resulted from an ontogenic error occurring around the time when the primitive canal closes [2]. Many of the affected children are asymptomatic at birth,

but neurological deterioration occurs mostly within the first 2–3 years of life due to spinal cord tethering by tissues that pass through it or by a thick terminal filum [46]. A duplicated filum terminale appears to be a rare finding in the absence of a split cord malformation [2] (Fig. 5.7). Since the embryogenic development of the filum terminale is distinct from that of the spinal cord, Pang et al.'s theory cannot explain the isolated finding of a duplicate filum. However, it has been speculated that a similar ontogenic error in the formation of the filum terminale resembles those manifestations seen in SCM [2].

Rizk et al. [2] reported two cases of duplicated filum terminale without split cord malformation: the first case was an incidental discovery during surgery when a resected thickened filum contained a smaller size filum, and the second case presented with a lumbar skin hemangioma found to have a duplicated filum terminale with fat signal in both structures. Masahito et al. [47] reported a case of a 2-year-old with split conus and filum terminale without an intervening septum [2].

Myxopapillary Ependymoma

Ependymomas are the second most common primary spinal neuroectodermal tumor in the pediatric population, accounting for 10–15% of spinal cord tumors [4, 48] (Fig. 5.8). A histologic variant of ependymoma, the myxopapillary type, is a slowly growing glioma believed to arise from the ependymal cells of the filum terminale internum or cauda equina [4]. The majority of such tumors occur during the fourth decade of life [48]. In rare cases, these tumors are located intrasacrally [4]. Some have speculated that in cases of sacrococcygeal ependymomas, the source of these tumors is in fact ependymal cells of the filum terminale externum; however, Tubbs et al. [4] did not observe such collection of cells in their cadaveric study. When found intrasacrally, these lesions may present as a presacral mass as they erode the anterior sacrum while producing thinning of its osseous margins [4]. This tumor was first described by Kernohan [49].

The microscopic component of the myxopapillary ependymoma is characterized by a papillary arrangement of cuboidal tumor cells around a vascular stromal core that undergoes mucinous degeneration [50]. It remains unknown whether the presence of a large number of glial cells within the filum terminale plays a role in the generation of these neoplasms; however, the presence of neuropil and its glial elements within the filum terminale, particularly the astroglial components, suggests a possible functional role for these components in spinal cord pathophysiology [1]. They are generally classified as WHO grade I lesions; however, occasionally CSF dissemination occurs, and multiple lesions are seen in 14–43% cases [51].

Clinically, myxopapillary ependymoma causes nonspecific symptoms such as radicular pain and back pain that are more pronounced at night and in recumbent positions [52]. Based on the amount of neural compression, patients may also develop motor, sensory (i.e., numbness), urinary (i.e., bladder sphincter

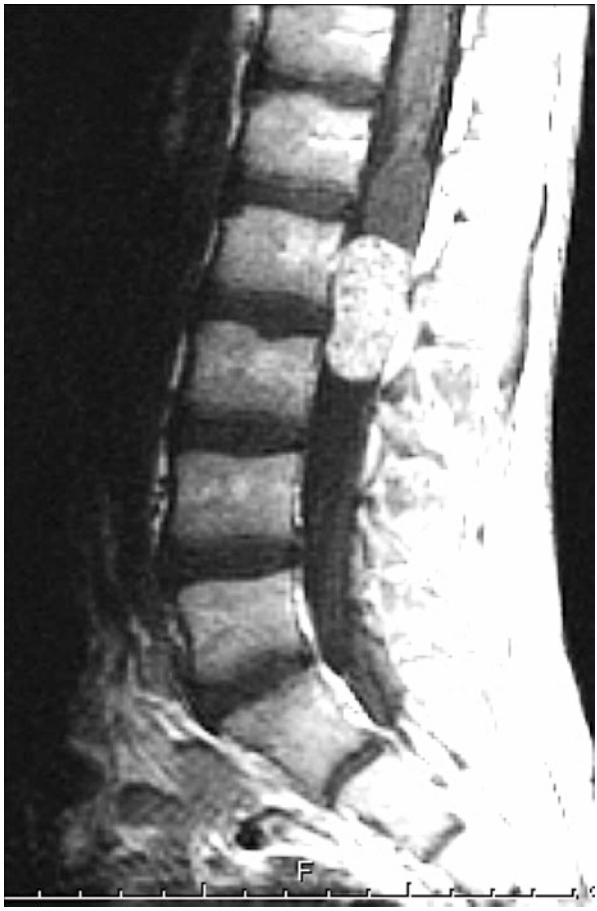

Fig. 5.8 Tumor of the filum terminale found to be a myxopapillary ependymoma

dysfunction), or gait problems. Patients often have a long history of nonspecific symptoms prior to clinical presentation due to the slow growth and well-circumscribed nature of these tumors [50, 52].

Ventriculus Terminalis

The ventriculus terminalis (VT) is a small ependymal-lined cavity within the conus medullaris and, for unknown reasons, is a region frequently involved in both glial and nonglial neoplasms [1, 3] (Fig. 5.4). VT is as a result of canalization and retrogressive differentiation during embryonic development. It has been described as a normal developmental phenomenon in newborns and pediatrics but is a rare pathology in adults, with only 21 cases reported to date [3]. Few have speculated on the development of VT. Some believe it's a cavity at the lower end of the conus medullaris that develops and grows along with the rest of the central nervous system. Occasionally, a remnant of the ventriculus may form a gelatinous mass on top of the

filum terminale that may be mistaken for a cystic tumor [1]. It has been hypothesized that the ventriculus terminalis is where Reissner's fiber (RF) terminates with the accumulation of neurosecretory substance [1]. Several authors have proposed these cavitations might be associated with trauma, vascular disturbance, inflammation, or compressive pathology of the spinal cord and may interrupt communication between the VT and the central canal [3, 26, 53].

Radiology

The normal filum is often so thin that it can barely be detected [42]. In diagnosing the tethered cord syndrome, the thick filum terminale is often defined as greater than 2 mm in diameter. The cutoff of 2 mm in diameter was derived from a series of normal myelographic measurements, first reported by Gryspeerdt [54]. The true normal diameter of the filum terminale diameter in children or adults remains unknown. Yundt et al. [55] measured the diameters of the filum terminale in vivo on 31 children undergoing selective dorsal rhizotomy for spastic cerebral palsy. Their data indicated that the filum terminale greater than 2 mm in diameter in children was abnormally thick [55]. This measurement of 2 mm has been cited in the literature for years and used as the upper limit of normal during intraoperative, myelographic, and MRI measurements [55].

Additionally, a spinal cord that terminates lower than the L2 or L3 vertebral body levels and a conus medullaris displaced posteriorly with the filum in contact with the dural sac at or near the L5 lamina have been established to aid in diagnosing this condition [28, 39]. This posterior placement of the filum may not be appreciated well on myelography unless supine films of the patient are obtained. On postmyelography CT, the thick filum appears as a small round filling defect extending through multiple sections [7]. According to Yamada [7], the thick filum has higher signal than CSF on T1 or proton density-weighted MRI images.

Fatty infiltration of the filum terminale may be seen as a clue to cord tethering. The fat appears as low attenuation on CT and bright on T1-weighted MRI sequences [7]. However, a fatty filum can be an incidental finding [2, 43] and is not considered diagnostic of tethered cord, as it is reportedly present in 5.8% of the normal population on postmortem examination. McLendon et al. [43] observed in their study of adipose tissue in the filum that masses with diameters greater than 0.2 cm would presumably be detected by CT scanning and be "false-positive" in the workup for a tethered cord. When a small collection of fat is noted on CT scan in symptomatic patients, water-soluble myelography followed by CT scanning or MRI is appropriate to exclude a tethered filum terminale [43].

Surgery

Hansasuta et al.'s [40] cadaveric study, in concordance with other anatomic studies in the literature [56, 57], has observed that fusion of the filum occurs most commonly at the S2 vertebral body level. Based on these observations, it has been

suggested the preferred surgical approach to untether the spinal cord is a S1 laminectomy, which should provide access to the filum in the majority of the patients [28, 39, 40]. However, it should be acknowledged that 15% of the filum may fuse above S1 and 11% may fuse off of the midline dorsally. This may impede localization of the filum, especially when performing surgery using an interlaminar approach with an endoscope [40, 58]. In these cases, surgeons may have to extend the exposure site in order to identify the filum. An additional partial or complete L5 laminectomy may need to be performed in order to expose the free non-fused filum [40].

Conclusion

Although usually just a small band found at the distal end of the spinal cord, the filum terminale's role in the tethered cord syndrome has become more apparent recently with an increased awareness of its potential to restrict spinal cord movement. Therefore, a thorough understanding of its anatomy, variants, and imaging characteristics is necessary for clinicians who view imaging or treat patients with the tethered cord syndrome.

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Clinical Presentations of the Occult Spinal Dysraphisms

6

Irene Kim and W. Jerry Oakes

Introduction

Occult spinal dysraphism (OSD) is comprised of a wide spectrum of closed congenital spinal anomalies, including lipomyelomeningocele, split cord malformation, neurenteric cyst, dermal sinus tract (DST), and tight filum terminale. These entities can occur in association with each other or even with open dysraphisms (myelomeningocele); that is, patients can have more than one expression of OSD. It should therefore come as no surprise that patients can present with an equally broad range of signs and symptoms. While some patients present at birth, others do not come to medical attention until adulthood. In this chapter, we will review the clinical presentation of patients with OSD (Table 6.1).

Table 6.1 Clinical presentation of OSD

Cutaneous stigmata
Motor weakness
Sensory disturbances
Orthopedic deformities
Urologic dysfunction
Infection
Pain

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Cutaneous Stigmata

Cutaneous abnormalities are present in 50–80% of patients with OSD and are frequently the reason for presentation for medical evaluation and investigation [1–6]. These stigmata are usually located in the midline and often occur near the level of the underlying intraspinal abnormality, which is usually in the lumbosacral region [2, 5]. It is not uncommon for a patient to have more than one cutaneous finding.

Focal hypertrichosis, commonly referred to as a hairy patch, is one of the most common cutaneous findings in OSD and is pathognomonic for split cord malformation. If hair is present, there is always some expression of split cord malformation. It may be mild, such as a duplicated central canal, but much more commonly, there is a true split cord. Focal hirsutism typically presents in one of two patterns, as a faun tail or silky down. A faun tail is a wide, usually triangular patch of coarse, terminal hair that can be several inches in length. Silky down refers to the presence of tufts of fine, soft, nonterminal hair or lanugo, often in a whorled pattern, which is usually limited to more discrete area in the midline (Fig. 6.1) [5, 7, 8].

A soft, non-tender, well-circumscribed subcutaneous mass is another common cutaneous finding (Fig. 6.2). The skin overlying these lesions may be normal or may exhibit another abnormality, such as hypertrichosis, hemangioma, or DST [5, 9, 10]. The vast majority of these subcutaneous masses are comprised of fat, which is seen in lipomyelomeningoceles, the most common type of spinal lipoma [9, 11]. In some cases, it can be quite subtle and go unnoticed without careful, deliberate inspection. In low-lying lipomyelomeningoceles, the mass may cause deviation or obscuration of the gluteal cleft. The majority is in the midline, but approximately one-third is paramedian in location. Asymmetric lesions are associated with a higher risk of neurologic deficit, typically in the lower extremity ipsilateral to the mass [2, 9, 11].

A small minority of subcutaneous masses are more fluctuant, which is seen in terminal myelocystoceles. These lesions are predominantly comprised of cerebrospinal fluid (CSF) but can also contain fat and neural elements and may swell with Valsalva maneuvers such as crying [10, 12]. Neuroenteric cysts can also occasionally present as a subcutaneous mass (Fig. 6.3).

Infantile hemangiomas are well-demarcated, vascular, typically raised lesions (Fig. 6.4). Flat capillary hemangiomas include port-wine stains, which are darker, purplish-red maculae with well-defined borders that can get darker over time, and nevus flammeus simplex, which are reddish-pink lesions with ill-defined borders [13]. A prospective study found that infantile hemangiomas >2.5 cm had a positive predictive value of 51.2% and a relative risk of 438 for OSD [14]. The association between flat capillary hemangiomas and OSD is less reliable than that between infantile hemangiomas and OSD [5, 13, 15, 16].

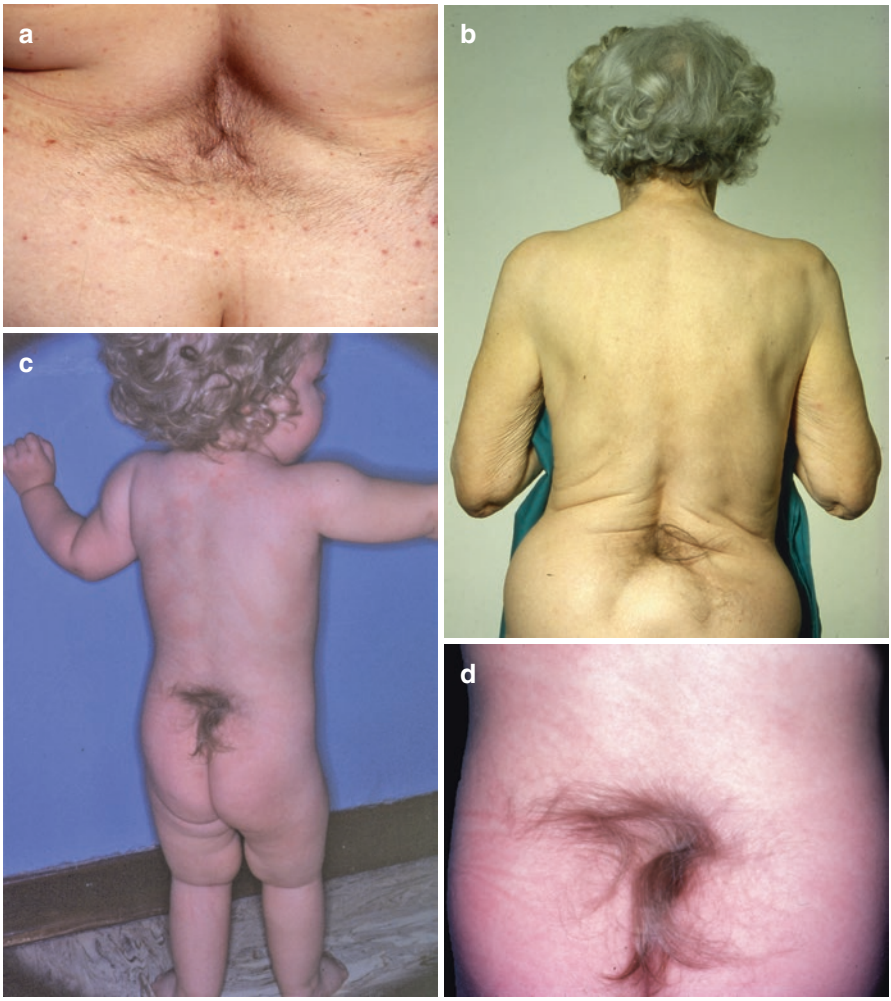
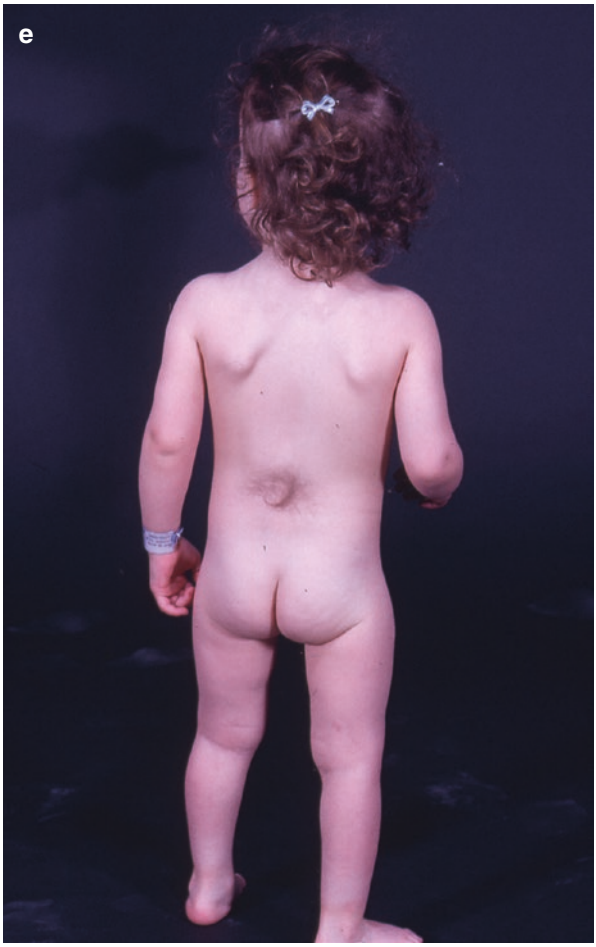


Fig. 6.1 (**a**) Adult with focal hirsutism in the lumbar region primarily in the midline. (**b**) Older adult female with evidence of a midline subcutaneous lipoma and focal hirsutism. This woman had draining osteomyelitis of her foot for more than four decades but had normal bowel and bladder function due to a split cord malformation with the lipoma involving only one hemicord. The other uninvolved hemicord maintained the neurological function of her bowel and bladder as well as of her other normally functioning leg. (**c**) Young child with typical focal hirsutism (faun tail) over the lower lumbar and sacral region. (**d**) Close-up view of the same child. (**e**) Another child with focal hirsutism at the thoracolumbar junction and normal neurological function

Fig. 6.1 (continued)



Hyperpigmented nevi and hypopigmented maculae have both been reported as being associated with OSD, but usually without further description of the lesions or histopathology [8, 17]. Aplasia cutis congenita is the congenital absence of the skin. It is typically found as a small, circular lesion in the vertex of the scalp, but several cases of aplasia cutis congenita in the midline in the lumbosacral region have been reported in association with OSD [18]. An atretic meningocele is a small area of dysplastic, thinned, scarified skin (Fig. 6.5). Sometimes referred to as a "cigarette burn" mark, it is often associated with an underlying meningocele manqué [13, 19, 20].

Caudal appendages, including skin tags, true tails, and pseudotails (Fig. 6.6), can also be seen in the presence of OSD [5, 17, 19]. A true tail, also called a persistent vestigial tail, is a midline appendage composed of skin, muscle, connective tissue, adipose tissue, blood vessels, and nerves. Usually located in sacrococcygeal region, it lacks vertebrae and is capable of spontaneous or reflexive movement.

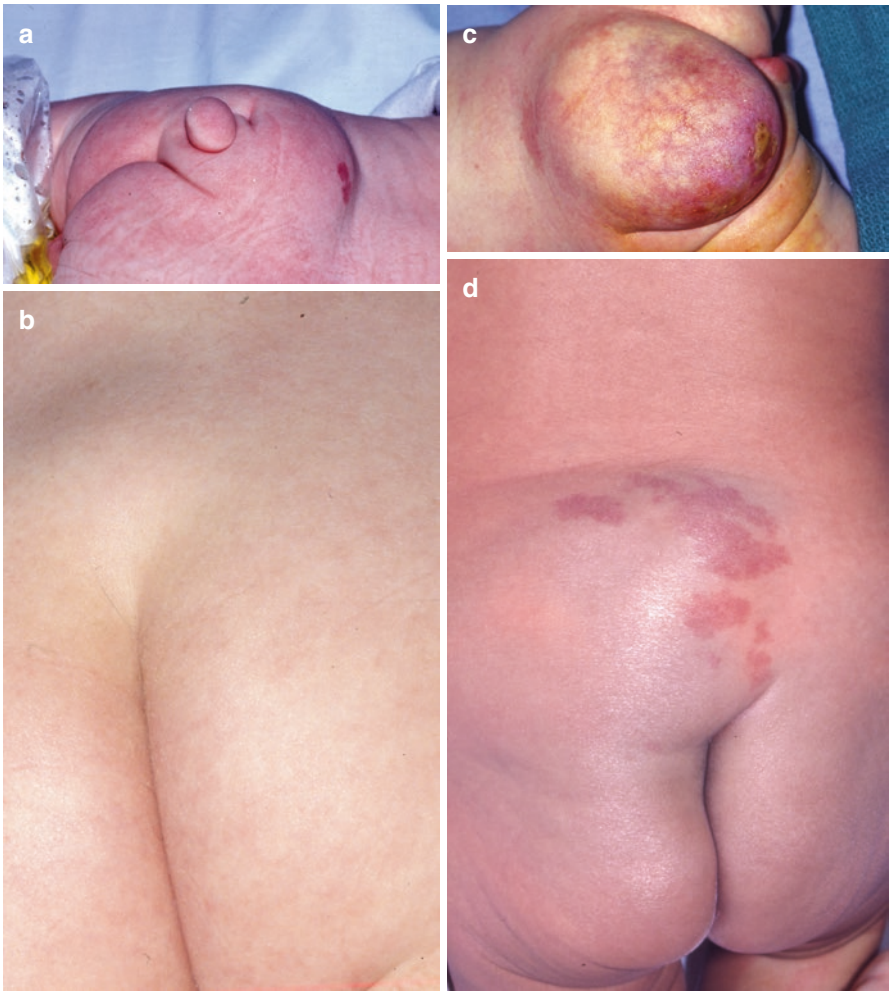


Fig. 6.2 (**a**) Neonate with a large lumbosacral lipoma and small capillary hemangioma on the superior right portion of the lipoma. Patient had normal neurologic and urologic function. (**b**) Subtle lipoma in an infant, again with normal neurologic function. (**c**) Subcutaneous midline lumbosacral mass which could be confused for a lipoma but in fact was a true myelomeningocele. There was little fatty involvement of either the neural elements or the surrounding dura. Shortly after this photograph was taken, the child developed a spontaneous CSF leak from the inferior left portion of the mass. The child was initially referred to the pediatric surgical service for a coccygeal teratoma. (**d**) Asymmetric lipoma of the lumbosacral region with superficial flat capillary hemangiomas and deviation of the gluteal crease because of the lipoma. The clinical exam in this child showed progressive loss of neurologic function of the left leg

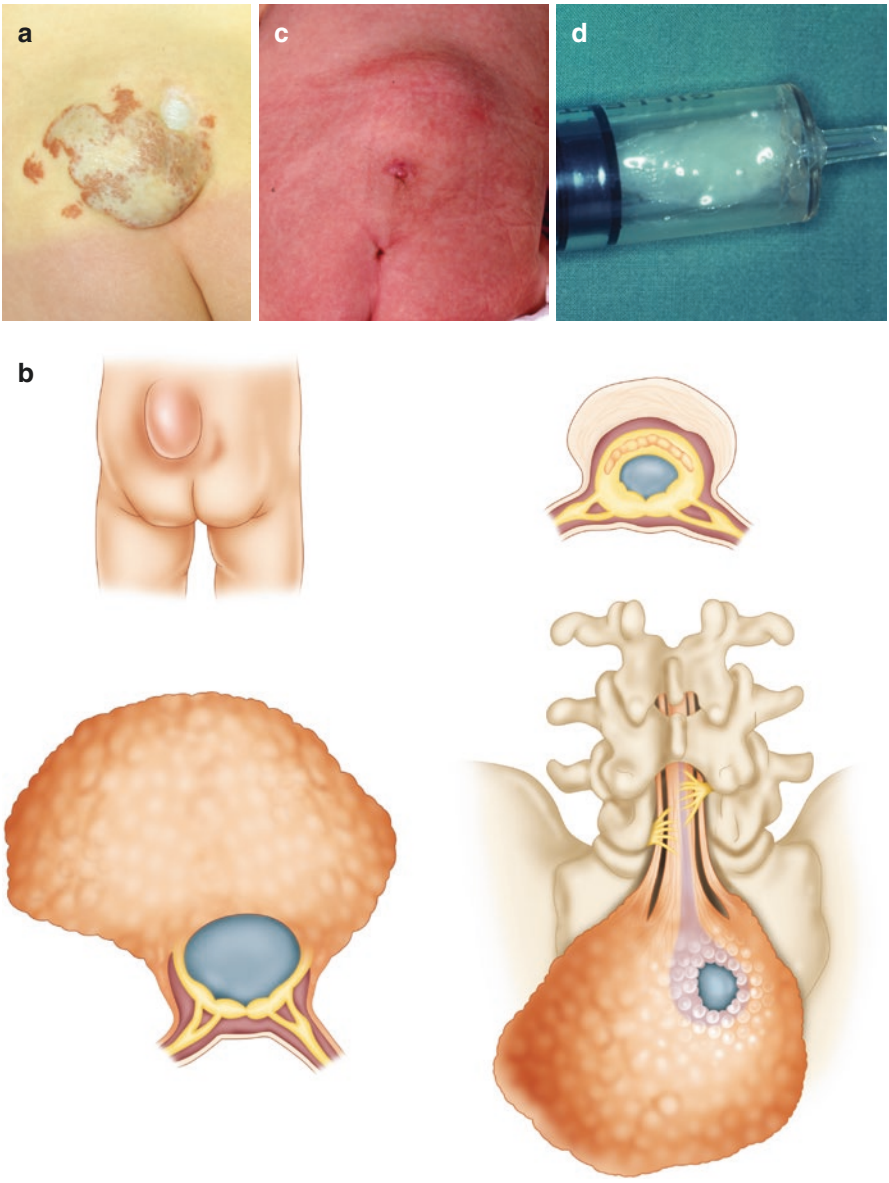


Fig. 6.3 (**a**) Newborn with subtle lumbosacral mass, superficial hemangioma, and a cleft over the dome of the lipoma. The cleft represents an area of dysmorphic skin overlying a CSF collection within the distal spinal cord typical of a lipomyelocystocele. (**b**) Illustration of the pathological changes of a lipomyelocystocele. (**c**) Infant with a midline lumbar mass superior to a dermal sinus tract. Although similar in appearance to a lipoma, this proved to be a subcutaneous neurenteric cyst. (**d**) Mucus obtained from the neuroenteric cyst at time of surgery

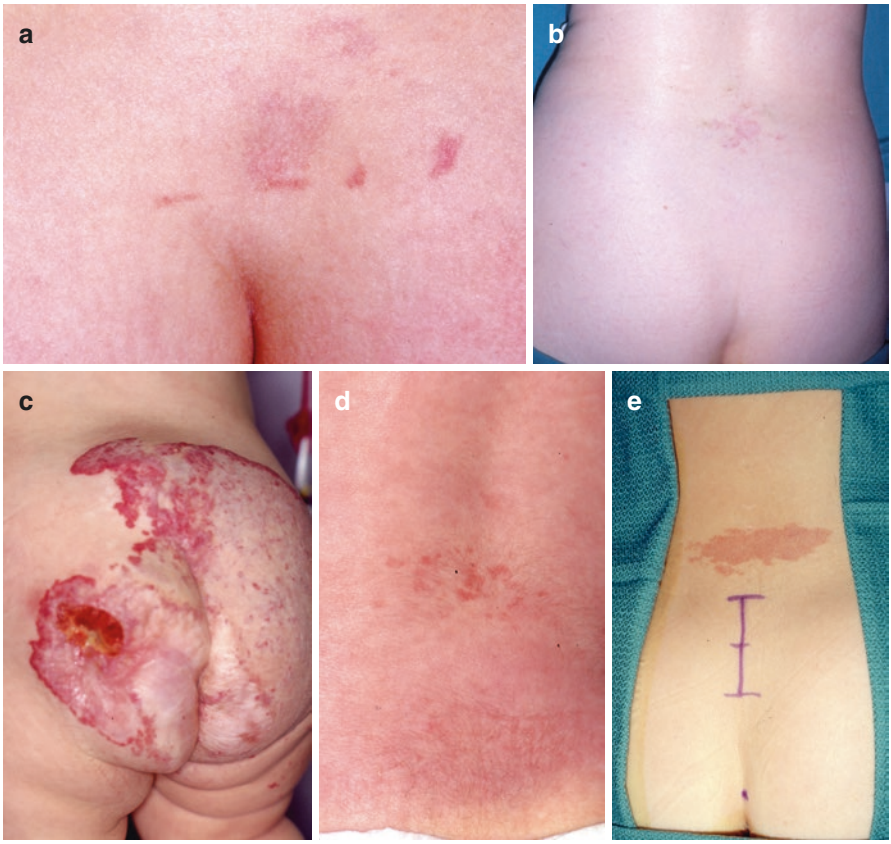


Fig. 6.4 (**a**) Subtle asymmetric flat capillary hemangioma in the lumbosacral region above the gluteal cleft. (**b**) More subtle hemangioma in the upper lumbar region in an adult with a thickened, taut filum terminale causing fixation of the distal spinal cord (tethered spinal cord syndrome). (**c**) Infant with a large lumbosacral lipoma and an overlying hemangioma in the process of involution. The superficial dermal layer has broken down in the inferior left quadrant of the hemangioma. Much of the velvety raised vascular aspect of the lesion on the right has involuted with time. (**d**) Spotty flat capillary hemangioma in an otherwise asymptomatic infant. (**e**) Broader flat capillary hemangioma in a symptomatic adult with tethered spinal cord syndrome

A pseudotail is composed of normal and abnormal tissues and is usually found in the coccygeal region. Often described as short or stump-like, it can include cartilage, fat, and teratomatous components. True tails occur more frequently in males, while pseudotails occur more frequently in females [5, 21].

A skin dimple or pit may indicate the presence of an underlying DST (Fig. 6.7). It is most often located in the midline anywhere along the spinal axis above the intergluteal crease, most commonly in the lumbosacral region. The dimple may be difficult to identify due to its small size, and intermittent drainage from the ostium is not uncommon. The underlying DST is composed of epithelial and fibrous tissue and typically courses rostrally as it goes deeper through the tissues [5, 13, 19, 22].

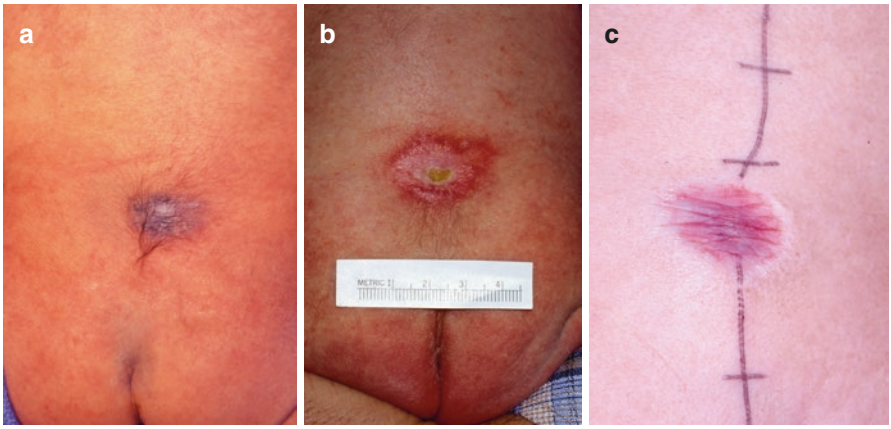


Fig. 6.5 (**a**) Neonate with a so-called cigarette burn over the mid-lumbar region. An area of hypertrichosis can be seen associated with the incomplete formation of the dermis. This lesion was so exquisitely sensitive to pressure that the infant was very uncomfortable lying on his back. (**b**) Newborn with a flat capillary hemangioma surrounding an area of incomplete dermis formation over the mid-lumbar region. This infant, too, had evidence of a thickened filum terminale and dural dehiscence directly under the central portion of the incomplete dermis. (**c**) Older infant with no capillary hemangioma but an area of distinct incomplete dermis formation, again associated with a thickened filum terminale. CSF is visible immediately under the thinned area of epithelium

At least 60% of DSTs terminate in the subarachnoid space. About half of all DSTs are associated with a dermoid or epidermoid cyst or inclusion tumor [23, 24].

It is important to distinguish the skin dimple associated with a DST from a simple coccygeal pit (Fig. 6.8). These congenital dermal sinuses are located below the level of the intergluteal crease. Present in 2–4% of the population, they are benign and do not require any further imaging or workup as they are not associated with OSD [3, 25].

Please refer to Chap. 4 for more detail and discussion on the cutaneous stigmata of OSD.

Infection

Infection may be the most serious and life-threatening clinical presentation in OSD and can be seen in patients with DST. The dermal sinus is a portal of entry for bacterial pathogens, which can result in bacterial meningitis. Aseptic chemical meningitis has also been reported secondary to spillage of epidermoid and dermoid cyst contents (desquamation of epithelium) into CSF spaces. In addition to meningitis, patients with DST can also present with subcutaneous, epidural, subdural, or intramedullary abscess formation or even infection of an associated inclusion tumor [22, 23, 26]. There has even been a reported case of patient who presented with a brain abscess as a manifestation of DST [27]. There should be a high level

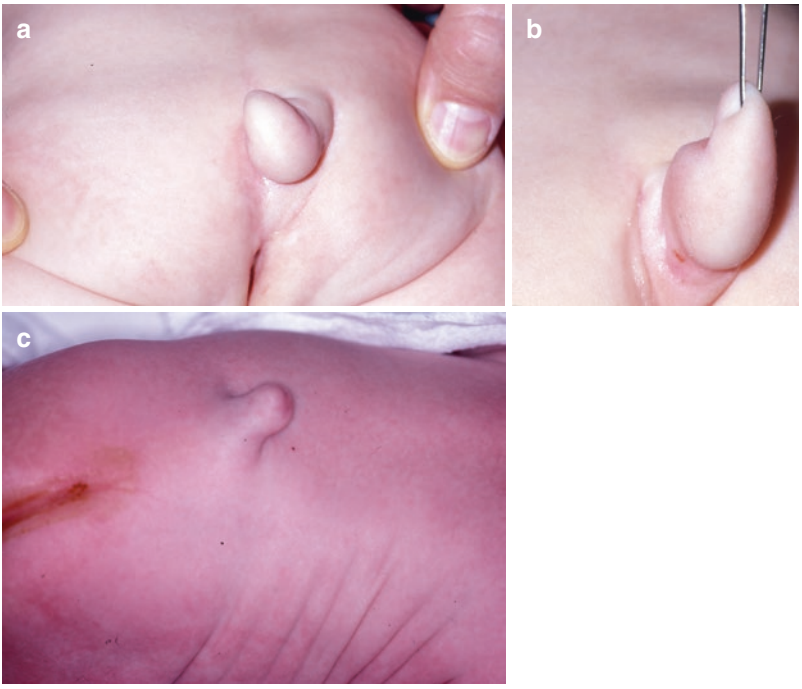


Fig. 6.6 (**a**) Asymmetric human tail in an infant with normal neurologic function but a low-lying conus secondary to a thickened and taut filum terminale. (**b**) A close-up view of the appendage. (**c**) Somewhat similar looking appendage from the lumbar region. However, this represents a skin-covered myelomeningocele rather than a human tail. Simple amputation of this will result in an increase in the neurologic deficit and CSF leak. A more formal myelomeningocele closure is necessary to address this lesion

of suspicion for DST in any young child who presents with aseptic meningitis or bacterial meningitis with an atypical organism, especially recurrent bouts of bacterial meningitis.

Reported organisms cultured from infected DSTs include *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus albus*, *Escherichia coli*, *Klebsiella*, *Proteus mirabilis*, *Proteus vulgaris*, *Bacteroides fragilis*, *Bacteroides vulgatus*, *Bacteroides melaninogenicus*, *Peptostreptococcus*, and *Peptococcus magnus*. Multiple organisms may be identified in as many as 20% of patients [24].

Patients typically present with recurrent or persistent fever after appropriate treatment of other potential sources (such as otitis media, sinusitis, bronchitis, etc.), neck or back pain, purulent drainage from the tract, erythema and induration surrounding the ostium, and other meningeal signs [22, 24]. Rarely, CSF leakage has been reported [28]. Although all patients with OSD can develop progressive neurologic dysfunction secondary to tethering of the spinal cord (see section "Neurologic Symptoms" below), neurologic deterioration secondary to an infected DST, most commonly paraplegia, is usually relatively rapid [22].

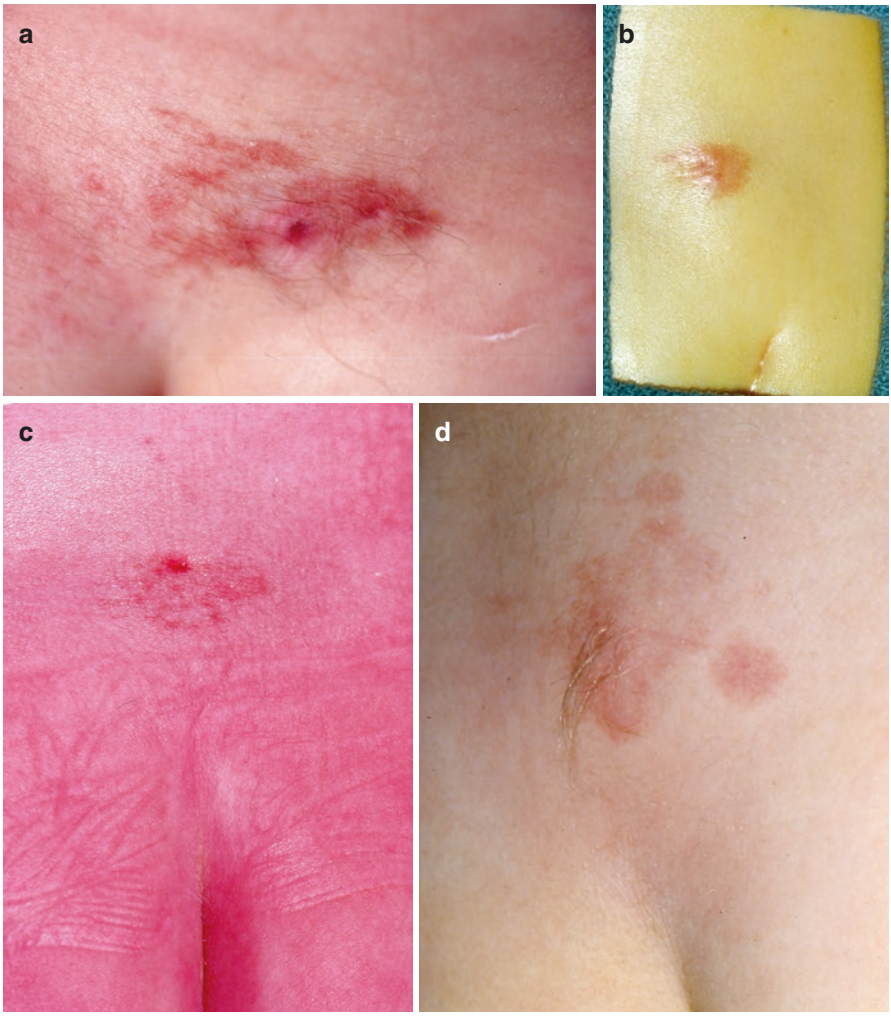


Fig. 6.7 (**a**) Dermal sinus tract with a paramedian opening to the right of the midline associated with a flat capillary hemangioma and limited but pathological hirsutism. (**b**) Asymmetrical dermal sinus tract to the left, again with a flat capillary hemangioma. (**c**) Midline dermal sinus tract in a child presenting with meningitis. (**d**) Flat capillary hemangioma and focal hirsutism in a midline dermal sinus tract. Note that all four of these lesions are above the gluteal crease

Recent series have indicated lower infection rates than older series, perhaps due to increased awareness of healthcare providers, especially primary care providers, about the cutaneous stigmata and sequelae of OSD. Although one recent series reported a 37.1% rate of meningitis, several other recent series report infection rates less than 15% [22, 23, 26, 29].

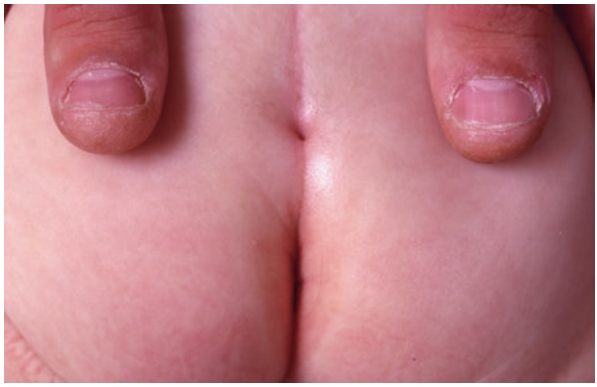


Fig. 6.8 Typical coccygeal pit located directly over the tip of the coccyx. The lesion is clearly within the gluteal crease and because of its location needs no further evaluation or consideration of surgical intervention. Lesions over the coccyx are not associated with surgically significant intradural pathology

Neurologic Symptoms

The natural history of OSD is one of progressive neurologic deteriorations. Upper motor neuron symptoms are due to tethering of the spinal cord. Pathologic fixation of the cord may result in repeated microtrauma to the spinal cord secondary to normal flexion and extension of the spinal column. It may also compromise the blood supply and oxidative neural metabolism to the spinal cord [2]. Lower motor neuron symptoms may be secondary to nerve root dysgenesis or local nerve root injury due to compression from a lumbosacral mass, such as a spinal lipoma, epidermoid or dermoid cyst, or abscess.

Neurologic deterioration tends to occur and progress during periods of growth as well as with repetitive flexion and extension movements of the spine. Symptoms are variable but can include progressive motor weakness, delayed gait development or gait deterioration, muscular atrophy, numbness, paresthesias, spasticity, and pain [1, 5].

Motor weakness is the most common symptom in the pediatric population, particularly in the lower extremities, and is often asymmetric. It may be accompanied by progressive muscle atrophy, which may be obscured by subcutaneous fat in infants. Patients may also develop increased tone and spasticity. Deep tendon reflexes can be hyperreflexic, normoreflexic, or hyporeflexic [1, 2, 5].

Sensory loss is less common and usually involves the buttocks, perineal region, and feet in a patchy, non-dermatomal distribution. Determination of altered or decreased pain appreciation in young children can be difficult, especially in the perineal area. Even experienced clinicians may misinterpret examination findings. Painless, trophic ulcerations can develop in these insensate areas. Nonhealing ulcers can lead to significant morbidity from additional complications such as osteomyelitis and toe amputations [1, 5, 30, 31].

Pain is much more prevalent in the adult population. It may be spontaneous, or it may be triggered by direct contact, activity, or trauma. Patients may experience

generalized low back pain, which may be exacerbated by progression of a scoliotic deformity. Tenderness of the subcutaneous mass is atypical in infant and children but can be seen in adolescents and adults. Pain in the lower extremities may be secondary to radiculopathy or may occur in a non-dermatomal distribution. Lhermitte sign has also been reported [9, 30, 32–34].

Hydrocephalus is a well-established sequela of infectious processes such as meningitis, ventriculitis, and/or arachnoiditis. It can also develop in association with intradural spinal tumors. Hydrocephalus in association with DST and/or dermoid tumors has rarely been reported. The mechanism for the development of hydrocephalus is not fully established but may favor a post-infectious or post-inflammatory phenomenon [22, 35].

Urologic Dysfunction

The progressive neurologic deterioration in OSD usually includes progressive bladder dysfunction. Urologic abnormalities tend to be more subtle than other symptoms but can range from a spastic, hypertonic bladder to a flaccid, hypotonic, overstretched bladder. Symptoms can include urinary frequency, urinary hesitancy, incomplete voiding, urinary incontinence, delay or regression in toilet training, and recurrent urinary tract infections. Subclinical findings on formal urodynamic testing can be an early indication of neurogenic bladder.

From a urologic standpoint, a flaccid bladder usually has a better prognosis than a spastic bladder, with less likelihood of upper tract damage. Detrusor hyperactivity leads to spasticity and hypertonia, causing elevated bladder filling pressures. Detrusor sphincter dyssynergia leads to elevated bladder-emptying pressures. This can result in a functional bladder outlet obstruction which can lead to vesicoureteral reflux, hydronephrosis, and, in severe cases, renal failure.

Chronic constipation is very common in patients with OSD. Bowel incontinence and sexual dysfunction are unusual and typically develop late in the progressive deterioration [1, 2, 5, 31, 36–38].

Please refer to Chap. 16 for more detail on the urologic aspects of OSD.

Orthopedic Deformities

The clinical presentation of OSD includes a wide spectrum of musculoskeletal abnormalities, predominantly involving the spinal column and lower extremities (Fig. 6.9). Sometimes referred to as the neuro-orthopedic syndrome, these deformities can be congenital, acquired, or iatrogenic. Congenital deformities include vertebral malformations such as hemivertebrae or congenital talipes equinovarus (CTEV), commonly known as club foot. Acquired deformities depend on the level of the neurological lesion but are frequently caused by muscular imbalance (i.e., flexors versus extensors). They may also develop as a result of habitual posturing or positioning. Some deformities may be iatrogenic, due to over or under correction of bony malformations or muscular imbalance [39, 40].

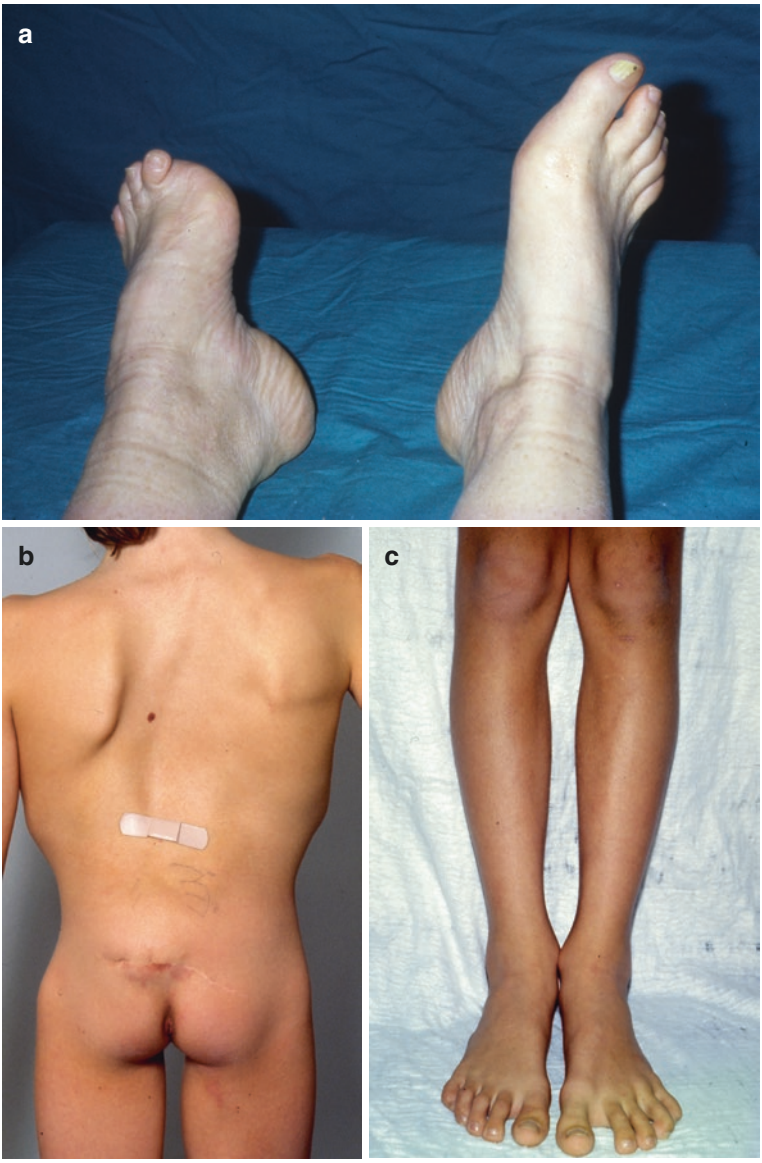


Fig. 6.9 (**a**) Elderly woman with split cord malformation who lost her left great toe from osteomyelitis because it was insensate. Note the high arch on the left compared to the right. Only one of the filum terminale was taut enough to produce a loss of sensory function causing the insensate left foot and the motor change resulting in the deformity of the foot. (**b**) Teenage male who had myelomeningocele repair elsewhere and had been followed in our spina bifida clinic for years. Note the well-healed small horizontal incision with loss of gluteal musculature. Over time, he progressively lost function in an asymmetric fashion. In point of fact, the cause of his decline was simple fixation of the distal cord from a tight filum terminale, not a myelomeningocele. (**c**) Minimally symptomatic child with split cord malformation with increased web space on the left foot as the only indication of a neurologic deficit. The patient also had no evidence of a neurogenic bladder at this point

Leg length discrepancy is one of the more commonly seen abnormalities. The abnormal, shorter lower extremity is usually weaker and may have an associated deformity. Foot deformities, including CTEV, pes cavovarus, pes cavus, calcaneus deformities, and vertical tali, are also frequently seen [39, 41, 42].

Scoliosis in OSD is multifactorial. While it is a manifestation of spinal cord tethering, other factors such as paraspinal muscular imbalance and vertebral anomalies such as segmentation anomalies, hemivertebrae, and butterfly vertebrae also contribute to the development and progression of scoliosis. Cord untethering may stabilize or even reverse the scoliotic deformity, particularly in patients whose scoliotic curves are <40° [13, 42–44].

Please refer to Chap. 16 for more detail on the orthopedic aspects of OSD.

Associated Syndromes

OSD has been associated with other congenital malformations and syndromes including anorectal malformations, Currarino triad, VACTERL (vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities) association, and OEIS (omphalocele, exstrophy, imperforate anus, and spinal defects) complex [4, 13, 45–47]. Please refer to Chap. 19 for more details on syndromes associated with OSD.

Conclusions

The clinical presentation of patients with OSD is immensely variable. There is consensus in the published literature that the natural history of diastematomyelia and lipomyelomeningocele, while somewhat unpredictable, is that of progressive neurologic deterioration [48–53]. By analogy, this is thought to extend to all forms of OSD, a fact which is somewhat bolstered by the preoperative clinical histories of patients with these other entities. It is critically important to be able to recognize the clinical syndrome of OSD, however subtle or obvious, as timely surgical intervention can prevent or, in some cases, reverse the natural history of neurologic decline.

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Adult Presentations/Outcomes of Occult Spinal Dysraphism

7

Anas Abdallah

Introduction

Occult spinal dysraphism (OSD) is defined as a group of congenital clinicopathological entities in the spinal cord. These pathological changes are underpinned by similar embryological causes and have multiple or single common forms of presentation. OSD generally appears in children, the most common OSD form in adults being tethered cord (TC) [1]. TC syndrome (TCS) is a neurological disorder caused by tissue attachments to the spinal cord at different levels. These attachments cause abnormal stretching of the spinal cord, limiting its movement. In some of these cases of congenital deterioration, a spinal cord with the conus in normal position can still be tethered by a thick filum or split cord. This limits its growth. As a result, patients can experience a wide spectrum of clinical presentations from asymptomatic to paraplegic [1–3]. TCS was described in 1976 by Hoffman et al. [4], who observed that the spinal cord was tethered via a thickened terminal filum to the sacral bones in 31 children and a noticeable neurological improvement followed release of the cord.

OSD syndromes are not rare pathological disorders, particularly in developing countries. The development of imaging technologies has increased the number of adults in whom OSDs such as congenital TCS are diagnosed. The incidence of OSD is not known. However, the incidence of neural tube defects is estimated at 0.17–6.39 per 1000 live births worldwide [5]. Occult spinal dysraphic lesions have been reduced in developed countries owing to folic acid supplementation during pregnancy and to prenatal diagnosis of dysraphic malformations, which often lead to termination of the pregnancy.

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Although the management of congenital OSD/TCS diagnosed in adulthood remains controversial, the results of recent clinical studies of surgical intervention in adults are encouraging [1, 6–11]. Herein, the presentation and surgical treatment outcomes of OSD diagnosed in adults are discussed.

Tethered Cord Syndrome in Adults

TCS is one of the most progressive forms of neurological deterioration resulting from spinal cord tethering by various dysraphic spinal abnormalities. Generally, the tethered cord entity is accompanied by one or more of OSD forms such as split cord malformations (bony septa or fibrous bands), intradural dermoid masses such as hamartomas or lipomas, tight or thick filum terminale, neurenteric cysts, meningocele manqué, scoliosis, syringohydromyelia, lipomyelomeningocele, dermal sinus tract, and diastematomyelia. These entities have a propensity for multiple expressions within the same patient (Case Study 1, Fig. 7.1) [1]. These malformations can be accompanied by malformations of other organs. Over our 12 years of experience,

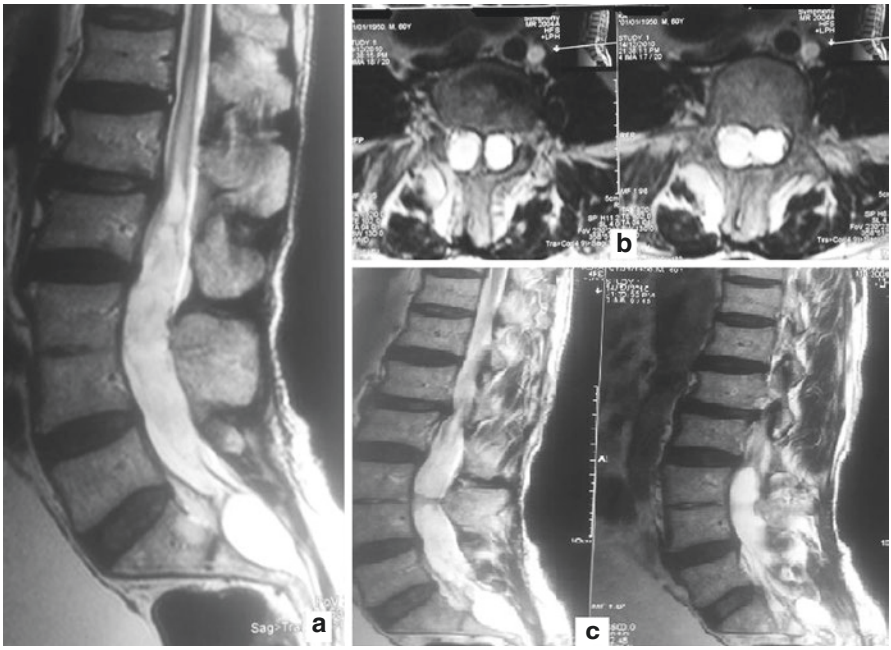

Fig. 7.1 A 61-year-old male patient presented with numbness and low back and leg pain: (**a**) T2-weighted sagittal MRI demonstrating cyst extends between L1 and S2. Note that L3 and L4 vertebral fusion anomaly (block vertebra) is apparent; (**b**) T2-weighted axial MRI showing that diastematomyelia extends between L2 and L4. Note split cord malformation as bony septum at L3 level and dermal sinus tract are apparent; (**c**) T2-weighted axial MRI demonstrating that filum terminale terminates at S1–S2 level (Case Study 1)

Table 7.1 Co-malformations detected in 31 adult TCS patients

Malformation	No. of patients	Percentage
Filum terminale (tethered cord)	31	100%
At L2 level	1	3.2%
At L3 level	4	12.9%
At L4 level	4	12.9%
At L5 level	10	32.3%
At S1 level	9	29%
At S2 level	3	9.7%
Diastematomyelia	13	41.9%
Vertebral fusion anomalies	13	41.9%
Split cord malformation	10	32.3%
As bony septum	6	19.4%
As fibrous bands	4	12.9%
Lipoma	8	25.8%
Scoliosis	8	25.8%
Syringohydromyelia	6	19.4%
Dermal sinus tract	6	19.4%
Foot anomalies (equinovarus, pes planus)	6	19.4%
Hypertrichosis	5	16.1%
Lipomeningocele	4	12.9%
Kidney malformations (hypoplastic, horseshoe)	4	12.9%
Skin hyperpigmentation	3	9.7%
Lipomyelomeningocele	2	6.5%
Chiari malformation	2	6.5%
Arachnoidal cyst	2	6.5%
Hydrocephalus	2	6.5%
Mitral valve prolapse	1	3.2%
Only tethered cord without co-malformation	3	9.7%

6 out of 31 operated adult TCS patients (25 patients were previously reported in 2 papers [1, 10]) had foot anomalies, and four had kidney malformations (Table 7.1).

The structure of the filum terminale is especially important in the development of TCS. Recently, Tehli et al. compared histopathological analyses of filum terminale between TCS patients and normal human fetuses. They observed adipose tissue, fibrosis, hyalinization, and meningothelial proliferation in filum terminale samples from TCS patients, but none of these in normal fetal samples. Elastic fibers were present in all TCS specimens and the adult cadaver, but not in the fetuses. Peripheral nerves, ganglion cells, and ependymal cells were observed in the normal human fetal filum terminale samples. Because these changes were not observed in fetuses, the authors suggested that this syndrome did not begin during intrauterine life [7, 10, 12]. According to this work, TC could be an acquired rather than a congenital syndrome.

Most adult patients experience TC during normal daily activity or mild static neurological deficits in childhood. The development of imaging technologies has increased the number of adults in whom congenital TCS is diagnosed. However,

unlike the pediatric population, adults may deny any significant symptoms and be unwilling to visit their doctors, so TCS, which is the most common form of OSD in adults, is usually diagnosed after progressive scoliosis, foot deformities, leg length discrepancy, or muscular atrophy, potentially increasing the chances of disability. In some cases, serious traumas such as traffic accidents or falling, as well as dynamic and static changes that occur in the spinal column (such as those during pregnancy), can aggravate the degenerative processes and induce back and leg pains.

Case Study 1 *A 61-year-old male was referred with low back and right leg pains. He had fallen 6 years earlier. His neurological examination was intact, except for weakness in his right leg distal muscles group of 4/5, right L2–L5 and S1 dermatomal hypoesthesia, neurogenic claudication, and the Babinski sign bilaterally evaluated as no response. MRI showed diastematomyelia at L2–L4, block vertebra at L3–L4, split cord malformation at L3 level as bony septum, and dermal sinus tract. A giant cyst extended between L1 and S2, while the filum terminale terminated at S1–S2 level* (Fig. 7.1). *Urodynamic study showed normocompliance normotonic bladder function. The patient underwent bony septum resection and duraplasty using total L3–L4 laminoplasty, followed by cystectomy using total S1 laminoplasty. Histopathological examinations revealed that the cyst was arachnoidal. The patient recovered quite well and was discharged after 3 days without complications. He was doing well on his postoperative 62nd-month doctor visit.*

Pathophysiology of TCS

TC coexists in open and occult forms of spinal dysraphisms [13]. The normal spinal cord is free in the spinal canal except for denticulate ligaments and nerve roots. As a result of TC, the spinal cord is tightly fixed. Therefore, there is no normal movement of the spinal cord when under pressure. During embryogenesis, the nascent spinal cord fills the spinal canal. Throughout the development of the fetus, the vertebral column grows faster than the spinal cord. Thus, the distal end of the spinal cord is located at the level of the first or second lumbar vertebral body in adults, but it can be located at the level of the third lumbar vertebral body in children. If an abnormality affects the nature of the spinal cord, such as split cord malformation, myelomeningocele, tight or thick filum terminale, diastematomyelia, or lipoma, the spinal cord is tethered [1, 14, 15]. This results in stretching of the spinal cord and causes neurological injury even in the fetus. At the time of birth, the spinal cord is normally located between the first and second lumbar vertebral bodies. After birth, continuing growth stretches the TC further; this injures the spinal cord both by directly stretching it and by interfering with its blood supply and oxidative metabolism [16]. If neurological findings are already presented, then further clinical deterioration can be anticipated. Adults with TC can show deterioration due to daily repetitive stretching and cumulative microtraumas during extension and flexion of the TC. A sudden flexion movement of the spine can also produce a symptomatic

onset of TCS [1, 10, 16]. Irreversible neuronal injury can result from sudden stretching of the already chronically stretched TC [16]. Yamada et al. demonstrated changes in spinal cord blood flow and oxidative metabolism following tethering of the spinal cord in both experimental animals and humans [16]. Usually a TC results in a low conus position. However, many cases of TCS have been reported with the conus at a normal level [1, 10, 13].

Sex and Age

The female preponderance in adult patients with TCS is well established in all published reports [1, 6, 9, 10, 13, 17, 18]. However, some authors have reported whole series of males, such as Akay et al., who reported nine young males with SCMs [19]. In agreement with previous publications, there was a female predominance of 18:13 (58%) in our patients. Klekamp reported in his series that 71.8% of his patients who underwent untethering were female [6]. Almost all congenital TCS is seen in children especially during the first year of life. The mean age of adult TCS patients in our experience is 32.1 ± 11.8 (18–68) years.

Clinical Presentation

Most adult patients with a TC have practiced their normal daily activities without complaint since childhood despite this congenital disorder. However, during adulthood, they become more aware of significant symptoms than the pediatric population. In some cases the symptoms of the TCS appear after a traffic accident or fall. Furthermore, physiological dynamic or static changes in the spinal column, such as those that happen during pregnancy, can aggravate the degenerative processes and induce back and leg pains.

Neurological deficits developed in adult TC patients are generally irreversible. Stretching of the conus medullaris and nerve roots can induce back pain, leg weakness, foot deformity, scoliosis, sensory loss, and/or bowel or bladder dysfunction [2, 3, 10, 13, 20]. Untreated TCS can progress in 27.5%, 40%, and 60% of cases at 1, 2, and 5 years after diagnosis, respectively [3]. In our series, the most common presenting symptom was pain, which was seen in 27 patients (87.1%); 20 patients experienced low back pain (64.5%), and 18 experienced leg pains (58.1%). The pain was followed by bladder dysfunction in 16 patients (51.6%) and muscular weakness in 16 (Table 7.2).

In TCS, stretching of the conus medullaris and nerve roots can induce back pain, leg weakness, foot deformity, scoliosis, sensory loss, and/or bowel or bladder dysfunction [2, 3, 13, 21]. In our experience during the last 12 years, 116 adult patients were diagnosed with TC after permanent or severe pain in their back and/or legs (incidentally) or in those experiencing serious urological complaints. Only 31 adult patients (26.7%) diagnosed as symptomatic TC were treated surgically after all investigations and full evaluation of their clinical status. Patients with tolerable

Table 7.2 The presenting symptoms of 31 adult TCS patients

Presenting symptoms	No. of patients	Percentage
Low back pain	20	64.5%
Leg pain	18	58.1%
Bladder dysfunction (incontinence or retention)	16	51.6%
Muscular weakness	16	51.6%
Numbness	8	25.8%
Unsteady gait	6	19.4%
Bowel dysfunction (fecal incontinence)	5	16.1%
Muscular atrophy	4	12.9%
Lumbar swelling	3	9.7%
Frequent lumbar skin infection	2	6.5%
Headache	1	3.2%
Vertigo	1	3.2%

Table 7.3 The clinical findings in neurological examinations of 31 adult TCS patients

Clinical findings	No. of patients	Percentage
Bladder dysfunction (incontinence or retention)	16	51.6%
Muscular weakness (motor deficit)	16	51.6%
Hypoesthesia	11	35.5%
Increased deep tendon reflex	8	25.8%
Extensor or indifferent Babinski	6/4	19.4%/12.9%
Loss of anal tone and sensation (fecal incontinence)	5	16.1%
Muscular atrophy	5	16.1%
Lumbar local tenderness	4	12.9%
Positive clonus	3	9.7%
Positive Hoffman	2	6.5%
Normal clinical findings	6	19.4%

pain, as seen in all of the adult patients with TCS in our series, were treated conservatively, with close follow-up (3-month periods) to preclude permanent new neurological deficits.

The patients have to undergo full neurological examination, especially those who experience low back and leg pains associated with urinary complaints. The most common clinical findings in our series were bladder dysfunction and muscular weakness, each seen in 16 patients (51.6%). Pathological (abnormal) responses to all of deep tendon reflexes, Babinski reflex, clonus, and Hoffman sign, noticed in 18 patients of our series (58.1%), are important indicators for checking the craniospinal MRI (Table 7.3). Because large numbers of new neurological deficits are expected in their age group, the surgical intervention rate was 100% among all children and adolescents with TCS referred to us (68 children and adolescents were diagnosed with TCS). Klekamp reported that 43 of his 85 (50.8%) adult patients with TCS underwent an untethering procedure [6].

Some authors suggest that the reversible symptoms associated with TCS are related to metabolic derangements and alterations in oxidative metabolism [16]. Not all neuronal injuries in TCS patients will necessarily be repaired after surgical intervention; the persistence of symptoms can vary depending on the severity of the

condition and the interval between presentation and initial treatment [1, 10]. If treated early, patients can recover from their neurological deficits. Chronic or excessive stretching of the spinal cord can lead to permanent disability. Although the period between initial symptoms and time of surgery ranged between 4 months and 25 years in our series, with an average of 5.2 years, early surgical intervention after increasing intensity of pain or severity of complaints gave good results; 64.5% ($n = 20$) of our patients recovered well.

Associated Malformations

Three of our 31 operated adult TCS patients were free of other malformations associated with TC (Case Study 2, Fig. 7.2). Therefore, malformations in patients with classic symptoms of TCS should alert physicians to refer such patients to neurosurgeons. Split cord malformations (SCMs) are mainly associated with TCS in adults [2]. Two types of SCM are distinguished on the basis of the state of the dural tube and the nature of the median septum (Table 7.1).

Some SCM cases show signs of TC but no spur is found in the malformations. This happens in type II SCM. The cleft is generally partial or incompletely split. Spina bifida is often present with the possible formation of hydromyelia and a thin fibrous band (FB) [15]. The management of TCS can change according to the associated SCM type [10]. For type I SCM, removal of the FB or bony septum (BS) can suffice (Case Study 1). If not, untethering is necessary. However, for type II SCM, removal of the FB should be followed directly by untethering.

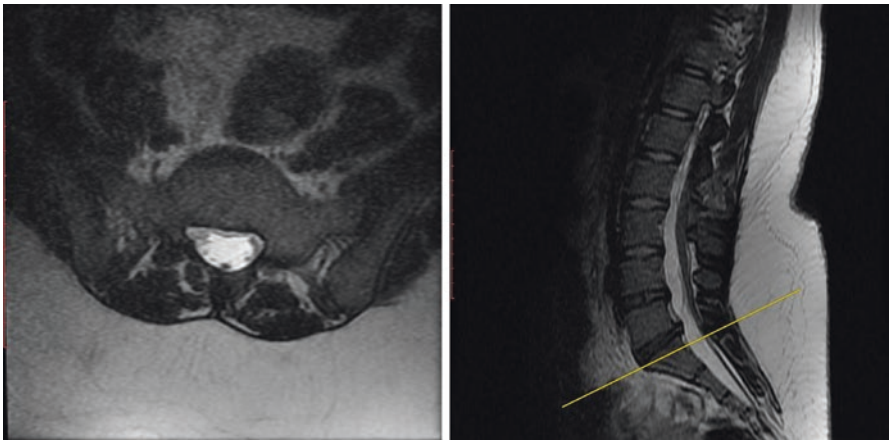

Fig. 7.2 A 21-year-old female presented with low back and leg pains for more than 5 years. Her neurological examination was intact, except rare loss of control of urination. T2-weighted MRI demonstrated that terminal filum terminates at L5 level. Right side: sagittal MRI demonstrated the tethered cord level; *yellow line* shows the cross-section at S1 level that axial MRI shows on the left side. Left side: axial MRI demonstrating tethered cord level (Case Study 2)

Case Study 2 *A 21-year-old female was referred to us with pain in her low back and both legs for more than 5 years. During the last month before the referral, she developed urinary incontinence. Her neurological examination was intact except for an infrequent loss of control of urination. MRI showed that the filum terminale terminated at L5 level* (Fig. 7.2)*. The patient underwent untethering using L5 laminoplasty. She recovered well and was discharged after 2 days without complications. The patient was doing well on her postoperative 24th-month doctor visit.*

Diagnosis of Adults with TCS

The diagnosis of OSD or TCS in adult patients is not well established until back and/or leg pain manifests. Several pathological conditions including fatty and thickened filum terminale, lipomyelomeningocele, meningocele, split cord malformation, diastematomyelia, and post-repair myelomeningocele can be responsible for TCS [1, 21]. It is well established that early surgical intervention of congenital TCS in children, whether symptomatic or otherwise, prevents additional neurosurgical deficits [2, 13, 22]. However, despite early diagnosis of these conditions, there remains an ongoing debate as to whether asymptomatic adult patients with TCS should undergo prophylactic surgery [1, 13]. According to Rajpal et al., the risk of new neurological deterioration in patients with congenital TCS increases with age. Therefore, Rajpal et al. suggest surgery for adult patients with TCS to protect them from developing new neurological deficits that could be permanent [9].

Although low back pain is the cardinal symptom for TCS, there are other presenting symptoms such as leg pain, anorectal and perineal pain, fatigue, recurrent bladder infections, progressive muscular weakness of the lower extremities, unsteady gait, patchy sensory loss, sacral sensory loss, progressive deformities (foot size discrepancies, foot and leg deformities, or scoliosis), bladder and bowel dysfunction (incontinence/retention), and sexual dysfunction (Table 7.2).

Midline cutaneous abnormalities are possible markers for ODS/TCS. Most patients with a TC have a discoloration or a lesion of some type on their skin in the midline [1, 10]. These skin markers are mostly located in the lumbosacral area. Therefore, full physical examination of suspected TC patients is recommended. Hairy patches/dimples (hypertrichosis), subcutaneous lipomas, myelomeningocele sac over the back, cutaneous hemangioma, port-wine stain, pigmentary nevus, and dermal sinus are the most common midline cutaneous markers associated with OSDs/TCS. After physical examination, careful neurological examination is required. The neurological findings in our 31 adult TCS patients are given in Table 7.3.

As with all OSD, TC in child or adult patients is determined by MRI, which shows a low level of the conus medullaris and other pathological findings such as thickened filum terminale, split cord malformation, or diastematomyelia that can be associated with TC (Fig. 7.3). Patients presenting with suspicious symptoms (back pain, leg pain, and/or urinary-fecal incontinence) (Table 7.2) associated with

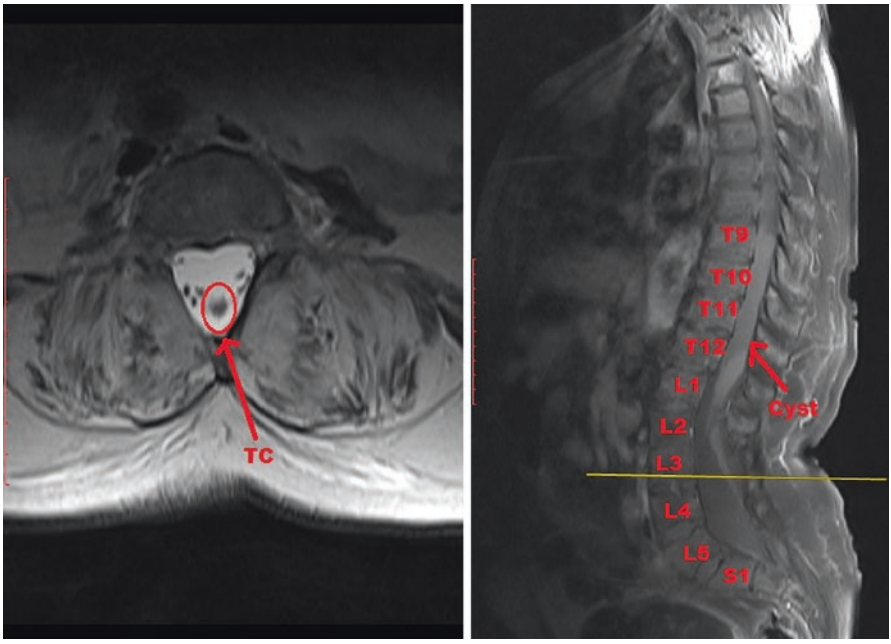

Fig. 7.3 A 68-year-old male patient presented with low back pain and progressive myelopathy. Right side: T1-weighted sagittal MRI with contrast enhancement demonstrating cyst extends between T9 and L2 and measures 12×86 mm. Note that L3 and L4 vertebral fusion anomaly (block vertebra) is apparent; *yellow line* shows the cross-section at L3 level that axial MRI shows on the left side. Left side: axial MRI demonstrated that filum terminale terminates inferior to L3 level (Case Study 3). *TC* tethered cord, *T* thoracic vertebral body, *L* lumbar vertebral body, *S* sacral vertebral body

any malformations or structural lesions such as lipomyelomeningocele, lipomeningocele, dermal sinus tract, cutaneous stigmata (hypertrichosis), scoliosis, or other system malformations (e.g., congenital heart disease, congenital kidney disease, or genetic syndrome) (Table 7.1) have to undergo detailed neurological and physical examinations, followed by craniospinal MRIs. Especially in patients with chronic low back pain that increases with static and dynamic movements, full physical and neurological examination has to be done first, and then plain X-rays of the spine have to be taken. After plain X-ray, lumbar MRI is the next least invasive imaging test for low back, back, or radiating leg pain. Lumbar MRI helps to reveal the level of the conus medullaris. If the TC is below the L2 level in an adult patient, craniospinal MRI is required before planning treatment.

The subtly differing properties of that signal from various tissues enable MRI to differentiate among organs and potentially to reveal contrasts between benign and malignant tissues (Fig. 7.3). MRI is excellent at demonstrating degenerative spinal changes such as arthritis, which can narrow the spaces through which the spinal nerves travel. In addition, it can determine herniation of the spinal discs between vertebral levels that can bulge and compress either the spinal cord or a nerve.

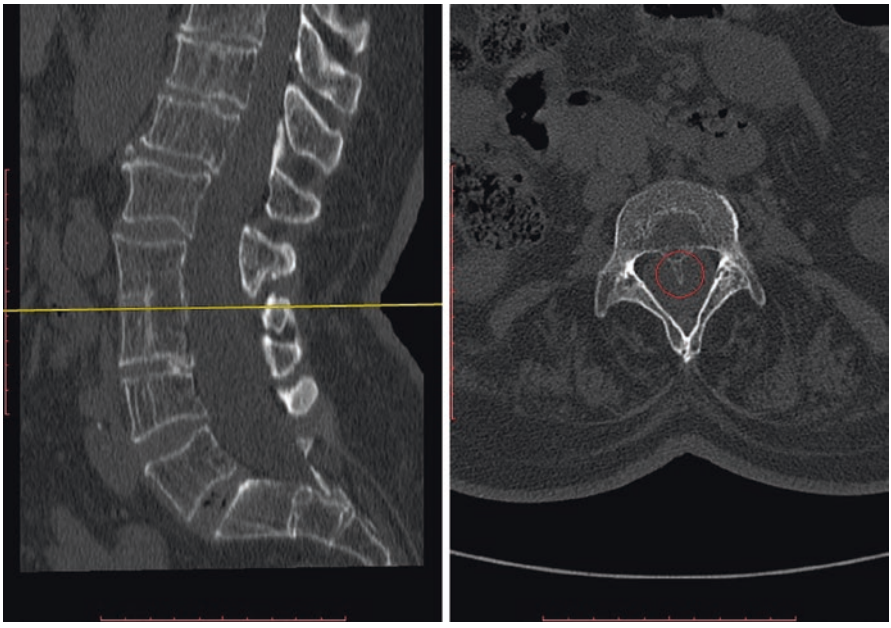

Fig. 7.4 CT imaging of Case Study 3. Right side: axial CT demonstrating posterior bony septum at L3 level. Left side: sagittal CT demonstrating block vertebra between L3 and L4 bodies; *yellow line* shows the cross-section at L3 level that axial CT shows on the right side

Computed tomography (CT) imaging can help define congenital bony anomalies better than MRI (Figs. 7.4 and 7.5) but has lost its prominence in the diagnostic assessment of TC and other OSD forms. High-resolution CT with thin slices and with reconstruction is useful in very complex OSD and to facilitate surgical planning. Three-dimensional CT can help to reveal scoliosis and bony markers to facilitate posterior instrumentation placement (Fig. 7.6).

Urodynamic study establishes the pressure-flow relationship between the bladder and urethra to define lower urinary tract function. This testing should assess the voiding phase of both bladder and urethral functions as well as the filling and storage phases. Simple urodynamic testing involves noninvasive uroflow study, obtaining a postvoid residual urine measurement, and performing single-channel cystometrography. In simple single-channel cystometrography, water is generally used as the fluid medium because it assesses the first sensations of filling, fullness, and urinary urge well. Bladder compliance and uninhibited detrusor phasic contractions can also be noted during filling cystometrography.

A video-urodynamic study is used to evaluate patients with incontinence. Radiographic contract substance is the fluid medium for such studies. Deterioration of kidney function secondary to high bladder pressure transmitted to the upper urinary tract has been seen in the setting of neurogenic lower tract dysfunction, which can arise in OSD cases and other neurogenic conditions. Urodynamic studies can reveal low bladder capacity and overflow incontinence and serve as predictors for good surgical outcomes [1, 10] or as a baseline for postoperative follow-up [13].

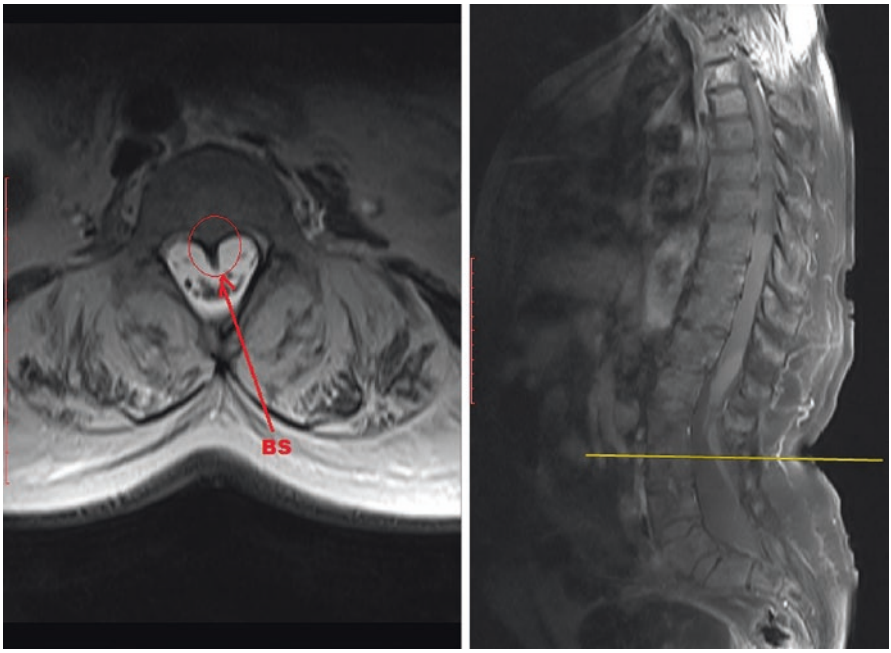

Fig. 7.5 MRI of Case Study 3. Right side: T1-weighted sagittal MRI with contrast enhancement; *yellow line* shows the cross-section at L3 level that axial MRI shows on the left side. Left side: T2-weighted axial MRI demonstrating posterior bony septum (BS) at L3 level (Case Study 3)

These urodynamic studies are useful because the therapeutic results are tied to understanding of the pathophysiological characteristics of a given case. Thus, surgeons can make a correct and complete diagnosis. Surgery on OSD cases presenting with urinary incontinence, if incorrectly diagnosed, can have substantial failure and high complication rates.

Unfortunately, urodynamic study is expensive and requires good specialized expertise and equipment, which can limit its availability. On the other hand, these studies are unphysiological in nature, and the reference ranges are wide. Therefore, the significance of the findings obtained must be assessed in association with the patient's symptoms. Studies that show abnormalities with no associated symptoms are not conclusive.

Case Study 3 *A 68-year-old male was referred to us with low back pain for 7 years and progressive myelopathy in both lower extremities for 4 months. He was operated on for inguinal hernia, cataract, and benign prostatic hyperplasia. His neurological examination was intact except for weakness in his right leg muscles group of 4/5 and weakness in his left leg muscles group of 2/5, bilateral L2–L5 and S1 dermatomal hypoesthesia, unsteady gait, joint position sense bilaterally evaluated as absent, bilateral positive clonus reflex, and the Babinski sign bilaterally evaluated as positive. MRI and CT imaging showed diastematomyelia at L1–L3, block vertebra at L3–L4, split cord malformation as an anterior fibrous band*

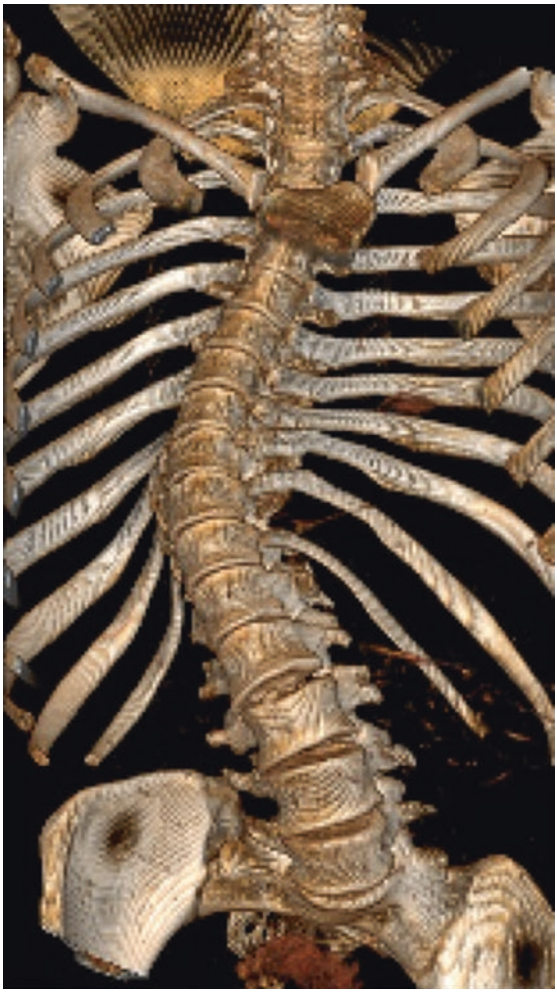

Fig. 7.6 Three-dimensional CT of Case Study 4 showing right curved thoracolumbar scoliosis

at level L2, and posterior bony septum at level L3. A giant cyst extended between T9 and L2 and measured 12x86 mm, while the filum terminale terminated at L4 level (Figs. 7.3, 7.4, 7.5, 7.7, and 7.8). *Urodynamic study showed normocompliance normotonic bladder function. The patient underwent laminotomy between T9 and L5 using a high-speed drill motor. The anterior fibrous band and posterior bony septum were resected at levels L2 and L3, respectively, followed by cystectomy, duraplasty, and total laminoplasty between T9 and L5 using nonabsorbable sutures* (Figs. 7.9, 7.10, and 7.11). *Histopathological examinations revealed that the cyst was arachnoidal. The patient was discharged after 7 days without complications. According to the neurological scoring system* (Table 7.4)*, his neurological examination at discharge showed improvement of pain intensity (from 2 to 3), motor weakness (from 2 to 4: left leg distal muscles group still unchanged), sensory disturbance (from 1 to 3), and gait ataxia (from 1 to 3). He had no*

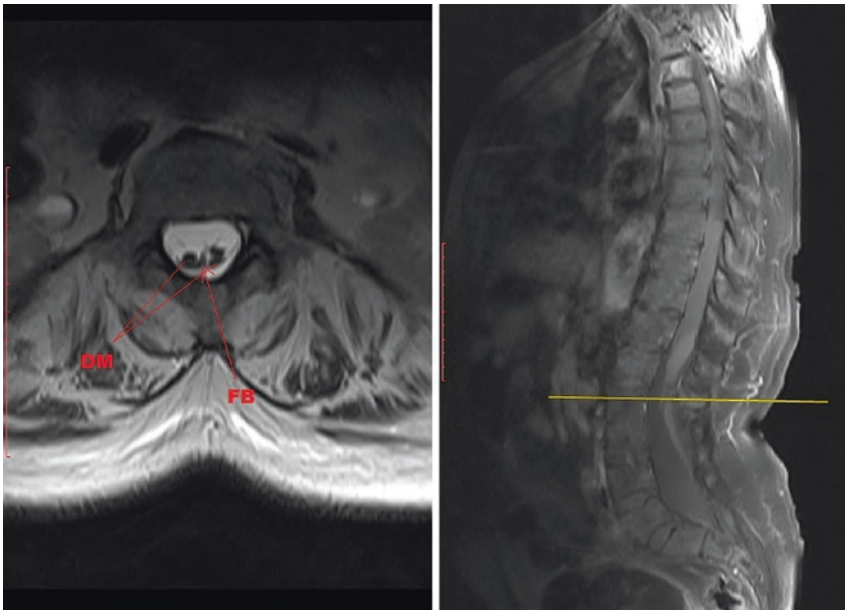

Fig. 7.7 MRI of Case Study 3. Right side: T1-weighted sagittal MRI with contrast enhancement; *yellow line* shows the cross-section at L2 level that axial MRI shows on the left side. Left side: T2-weighted axial MRI demonstrating anterior fibrous band (FB) at L2 level (Case Study 3). *DM* diastematomyelia

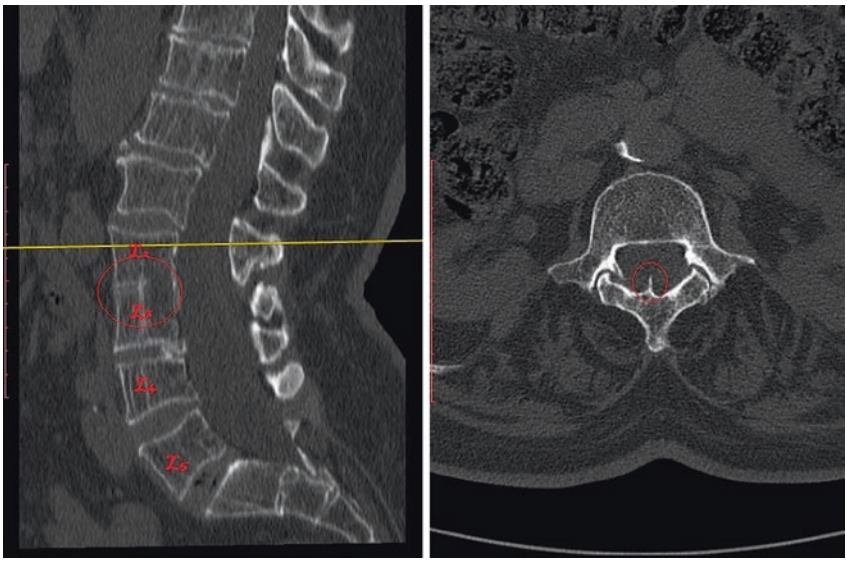

Fig. 7.8 CT imaging of Case Study 3. Right side: axial CT demonstrated anterior FB at L2 level. Left side: sagittal CT demonstrated block vertebra between L3 and L4 bodies; *yellow line* shows the cross-section at L2 level that axial CT shows on the right side. *L* lumbar vertebral body

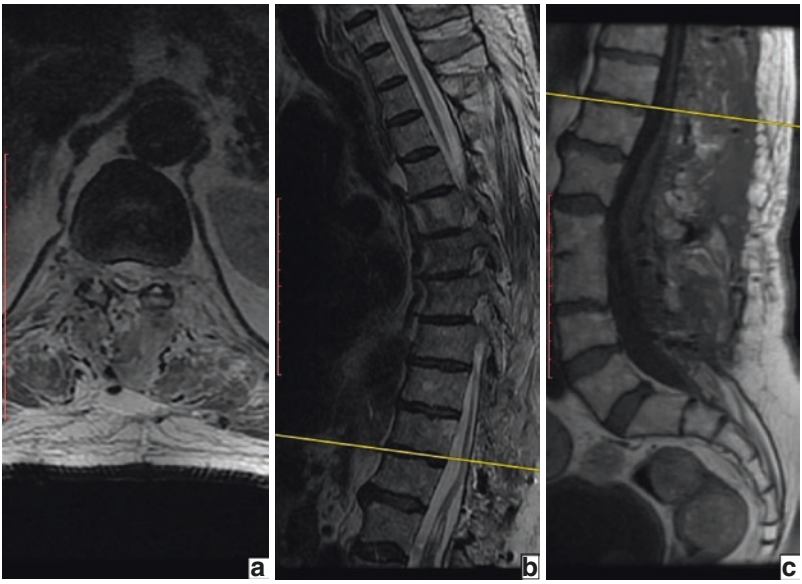

Fig. 7.9 Early postoperative MRI of Case Study 3: (**a**) T2-weighted axial MRI demonstrated axial cross-section at T11–T12 level; (**b**) T2-weighted sagittal thoracolumbar MRI demonstrated cyst was excised totally; (**c**) T1-weighted sagittal lumbar MRI showed cystectomy and postoperative changes; *yellow lines in* (**b**, **c**) show the cross-section at T11–T12 level that axial MRI shows in (**a**)

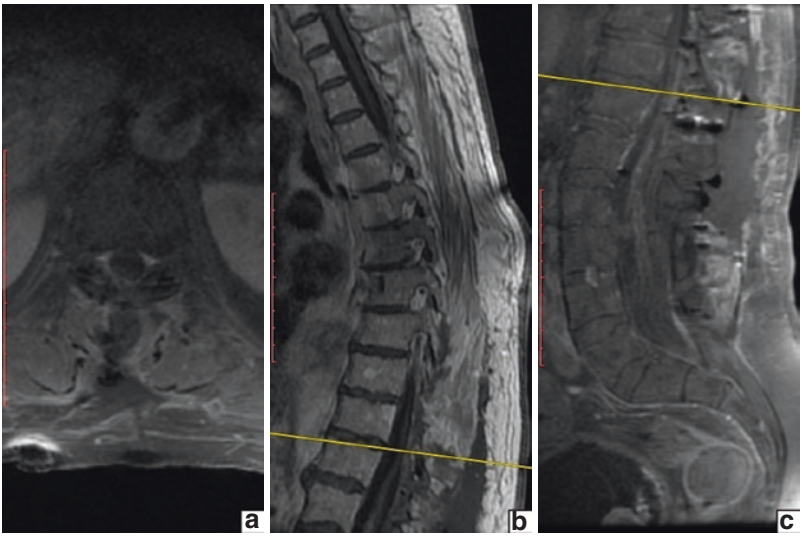

Fig. 7.10 Early postoperative MRI of Case Study 3; (**a**) T1-weighted axial MRI with contrast enhancement demonstrated axial cross-section superior to T12 level; (**b**) T1-weighted sagittal thoracolumbar MRI without contrast enhancement demonstrated cyst was excised totally; (**c**) T1-weighted sagittal lumbar MRI with contrast enhancement showing cystectomy and postoperative changes, *yellow lines in* (**b**, **c**) show the cross-section superior to T12 level that axial MRI shows in (**a**)

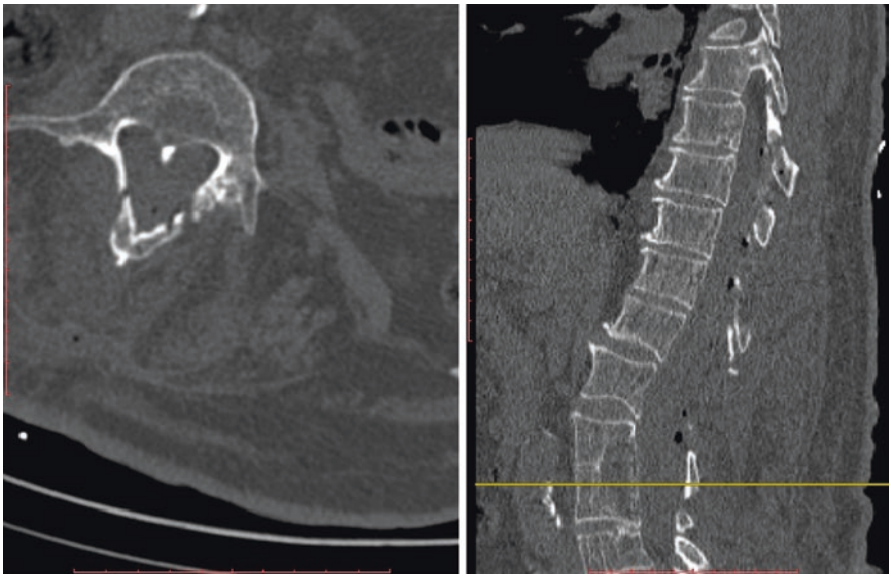

Fig. 7.11 Early postoperative CT imaging of Case Study 3. Right side: sagittal CT demonstrated total L3 laminoplasty using nonabsorbable sutures; *yellow line* shows the cross-section at L3 level that axial CT shows on the left side. Left side: axial CT demonstrating laminoplasty

Table 7.4 Neurological scoring system

Score	Pain intensity	Sensory disturbance, dysesthesias	Motor weakness	Gait ataxia	Sphincter function
5	None	Normal	Full power	Normal	Normal
4	Slight, no medication	Present, not significant	Movement against resistance	Unsteady, no aid	Slight disturbance, no catheter
3	Tolerable w/ medication	Significant, function not restricted	Movement against gravity	Mobile w/ aid	Residual in urodynamic studies, no catheter[a]
2	Insufficient control w/ medication	Some restriction of function	Movement w/o gravity	Few steps w/ aid	Rarely incontinent
1	Severe despite medication	Severe restriction of function	Contraction w/o movement	Standing w/ aid	Frequent catheter
0	Incapacitating	Incapacitated function	Paralysis	Paralysis	Permanent catheter

Data from Sofuoğlu et al. [10]
w/ with, *w/o* without
[a]Modified according to our protocol

complaints of sphincter dysfunction. The patient was sent to a physiotherapy center. His neurological examination was quite improved on his postoperative 6th-month doctor visit.

Other Adult OSD Forms

Spinal anomalies common to OSD include fatty and thickened filum terminale, split cord malformation, diastematomyelia, lipomyelomeningocele, meningocele, dermal sinus, tight filum terminale, neurenteric cysts, terminal myelocystocele, and meningocele manqué (Table 7.1).

Split Cord Malformation (SCM) and Diastematomyelia

Split cord malformations (SCMs) are mainly associated with TC in adults [2]. They are divided into two types on the basis of the state of the dural tube and the nature of the median septum: type I (i.e., diastematomyelia with septum) (Figs. 7.1 and 7.3) and type II (i.e., diastematomyelia without septum) (Fig. 7.12). The former type usually coexists with scoliosis and TCS. Cutaneous stigmata (hemangioma), skin discolorations, and hypertrichosis are characteristic features of type I SCM. Butterfly vertebrae, block vertebra, hemivertebrae, and spina bifida are the vertebral abnormalities that can be associated with this type [1, 14]. The BS (Figs. 7.4 and 7.5) or FB (Figs. 7.7 and 7.8) midline septum splits the spinal cord into two tubes each containing a hemicord. Beyond the BS, which can occur in either the thoracic or lumbar regions, the two hemicords adhere to each other and return to a normal anatomical position. Some cases of SCM show signs of TC though no spur is found in the malformation. This happens in type II SCM. The cleft is generally partial or incompletely split. Spina bifida is often present with the possible formation of hydromyelia, and a thin FB can form [15].

Diastematomyelia also accompanies SCM (Figs. 7.1 and 7.3). Diastematomyelia refers to the splitting of the spinal cord, conus medullaris, or filum terminale in the sagittal plane into two not necessarily equal hemicords [15, 19, 21]. A thick cutaneous hairy patch usually overlies the region of the diastematomyelia [1, 14, 15]. Diastematomyelia accounts for up to 44% of OSD cases [1]. Vertebral fusion anomalies and scoliosis are almost always associated with it. Tethering can result from dorsal or ventral tethering bands between the hemicords and the dura or from a thickened filum terminale.

In adult OSD, craniospinal MRI, particularly axial sections, axial sectioned CT, or CT myelography, is useful for demonstrating the hemicords and median septum (Fig. 7.1). As we previously explained, neurosurgeons have to decide about surgical intervention according to patients' complaints and neurological examination when confirmed by MRI and urodynamic study. Surgery can involve resecting the median septum and dividing a thickened filum and dorsal tethering bands or releasing the spinal cord if it is tethered. In our experience, resection of

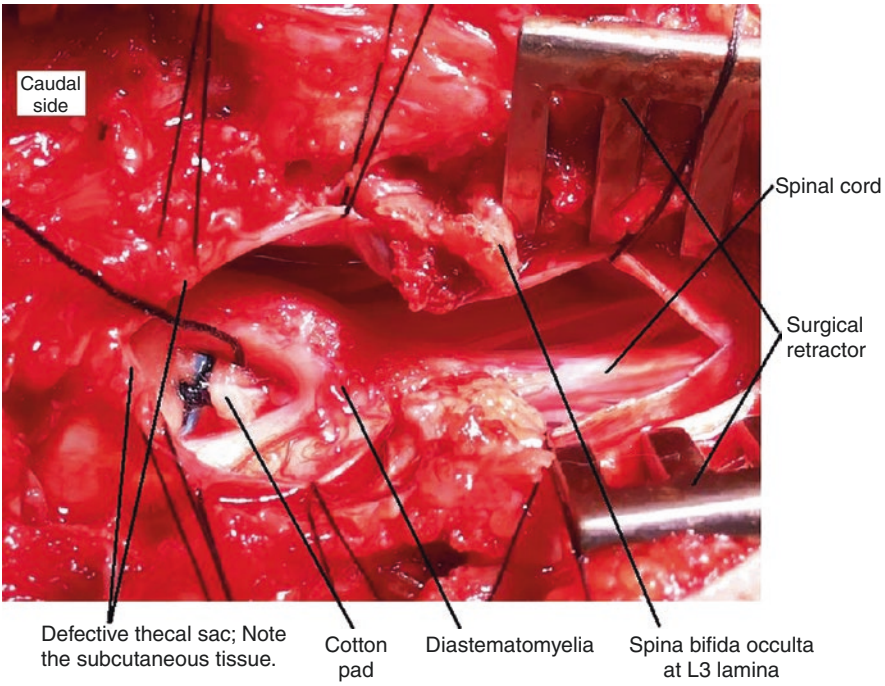

Fig. 7.12 Photo had been taken during the operation showing spina bifida occulta at L3–L4, diastematomyelia at L3, and the thecal sac terminated in the skin at the L3–L4 level. Note the subcutaneous fatty tissue in the caudal part of the dura (lipomeningocele). There was no bony septum or fibrous band between the hemispinal cords (SCM type II)

the median FB or BS in four patients (12.9% of the total) who presented with TCS without releasing the TC relieved or improved the neurological and urological symptoms.

Lipomyelomeningocele, Lipomeningocele, and Spinal Lipoma

Fatty accumulations within the spinal cord are common lesions associated with TC and take one of four forms: lipomyelomeningocele, lipomeningocele, spinal lipoma, and fatty filum. Meningocele is a type of spina bifida cystica characterized by the herniation of meninges through an abnormal opening in the spinal column. Myelomeningocele is another type of spina bifida cystica characterized by the herniation of spinal cord contents and meninges through an abnormal opening in the spinal column. When a lipoma covers the sites of meningocele and myelomeningocele, they are called lipomeningocele (Fig. 7.12) and lipomyelomeningocele, respectively.

Lipomyelomeningocele is a subcutaneous malformation within the spinal cord that extends through a defect of the lumbosacral fascia, lamina, dura, and pia into a

low-lying spinal cord [15]. Although it is the most common form of spinal lipoma, patients with lipomyelomeningoceles usually present to healthcare centers within the first few months to years of life. Therefore, these lesions are rarely seen in adult patients [1]. Lipomyelomeningocele is a lipoma of the conus medullaris [23].

The relative anatomy of the lipoma and neural tissues distinguishes three types of lipomyelomeningocele: dorsal, transitional, and caudal. In the dorsal type, lipomas have an area of attachment to the dorsal spinal cord at the splitting point in the lumbar or lumbosacral levels and are continuous with the subcutaneous tissue. In the transitional type, lipomas have attachments that extend beyond the splitting area down the conus medullaris, with a less distinct lipoma-cord interface. In this type, lipomas can extend through a dural defect. In the caudal type, lipomas arise predominantly from the caudal side of the conus medullaris.

Spinal cord (intradural) lipomas are rare intramedullary lesions almost always found within the thoracic spinal cord. They are not associated with cutaneous or bone malformations and often present with symptoms of spinal cord compression. The fatty thickened filum involves fatty infiltration into the whole length or part of the filum terminale. The fat within the thick filum can be diagnosed by MRI. The occurrence of incidental fat within the filum terminale in the normal adult population has been estimated to be 3.7% in cadaveric studies and 1.5–5% in MRI studies [23].

Fatty accumulations can be diagnosed by the associated subcutaneous lumbosacral masses found in almost all patients or by sagittal and coronal MRI. Surgery on the symptomatic patient has been advocated by many authors to prevent further decline in neurological status [1]. For lipomyelomeningoceles and lipomeningoceles, the aim of surgical intervention is to reconstruct the neural tube and then to repair the thecal sac to reformat the subarachnoid space (Fig. 7.13).

In our adult OSD cases, 2 out of 31 (6.5%) had lipomyelomeningocele, 4 (12.9%) had lipomeningocele, and lipomas were seen in 8 (25.8%). The operation for fatty accumulations has been significantly advanced by IONM and laminoplasty. Once

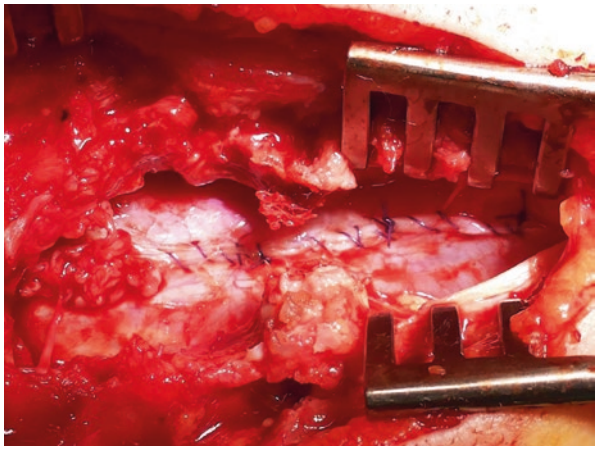

Fig. 7.13 Intraoperative photo shows duraplasty was performed using 5.0 absorbable sutures after exploring the spinal cord. Thus, the thecal sac was repaired

the spinal cord has been released, we recommend closure and enlargement of the dura with an allograft material to reduce the risk of re-tethering. Surgery for a lipoma of the filum terminale in the symptomatic patient has been recommended [1, 6, 10]. Surgery for an asymptomatic lipoma of the conus medullaris is still controversial [10].

Tight Filum Terminale Syndrome

This syndrome refers to TCS in a patient with a low-lying conus medullaris. In almost all such patients, the tip of the conus medullaris lies inferior to the L2 body. In this TCS, the filum terminale exceeds 2 mm in diameter, and there are no other tethered malformations. In 86% of patients, the tip of the conus medullaris lies inferior to L2. The tight thickened filum terminale and the low-lying conus can be visualized on MRI [23].

Terminal Myelocystoceles

These malformations are rare forms of OSD, the elements of which include expansion of the central canal of the caudal spinal cord by a cerebrospinal fluid (CSF)-containing terminal cyst, which is itself surrounded by an expanded dural sac. Patients harboring these lesions typically have no bowel or bladder control and possess poor lower-extremity function. Therefore, such patients are diagnosed in early childhood. These malformations are associated with a lipoma or multiple congenital genitourinary and orthopedic defects such as omphalocele, cloacal exstrophy, imperforate anus, renal abnormalities, ambiguous genitalia, pelvic deformity, and talipes equinovarus. In such OSDs, tethering results from the attachment of the myelocystocele to the inferior aspect of the spinal cord [23]. Terminal myelocystocele, like all OSDs, can be diagnosed by MRI. The aim of surgery is to separate the spinal cord from the fluid-filled terminal myelocystocele, reconstruct the neural tube, and then repair the dura to reformat the subarachnoid space.

Spinal Neurenteric Cysts

These cysts are rare congenital malformations formed by entrapment of endodermal tissue between a split notochord. Such cysts can be extraspinal with mediastinal or abdominal extension, or they can be intramedullary. They are frequently associated with spina bifida and can occur with no associated dysraphic lesions. Patients with these lesions can present with acute progressive signs as a result of spinal cord compression. A neurenteric cyst can be diagnosed by MRI. The aim of surgery is to remove the cysts totally. Subtotal resection of them increases the recurrence rate [23].

Dermal Sinus Tract

A dermal sinus tract appears as a midline dimple in the lower lumbar and lumbosacral region (Fig. 7.1). Patients with dermal sinus tract are usually referred to neurosurgeons or general surgery with recurrent infection in the affected area, which can present as meningitis. The dermal sinus tract can extend from the skin surface to the dura, subarachnoid space, or the spinal cord, thereby causing tethering [23]. It can be visualized by MRI or CT myelography.

Meningocele Manqué

Meningocele manqué refers to a dysraphic lesion of dorsal tethered bands composed of fibrotic or atretic neural tissue connecting the spinal cord to the dura or surrounding structures. These lesions are usually found incidentally during surgical exploration for other OSDs, and they can occur far from the site of obvious tethering. These tethered bands are almost always found at the site of diastematomyelia. The aim of surgical intervention is to remove these bands. Meningocele manqué can be visualized by MRI [23].

Case Study 4 *A 19-year-old female was referred to us with low back pain, uncontrolled leg contractions, and unsteady gait for 6 years and progressive myelopathy in the left leg and urinary-fecal incontinence for 4 months. She had had spinal malformations since her birth. She was referred to another healthcare center after urodynamic study that showed low bladder capacity and overflow incontinence. The urological surgeon recommended a Foley catheter three times and oxybutynin 5 mg twice a day. HerPlease check if edit to sentence starting "Her neurological examination…" is okay. neurological examination was intact except for weakness in her left leg muscles group of 2/5, ataxic gait, walking only a few steps with aid, left positive clonus reflex, and deep tendon reflexes increased in the left leg. MRI and CT imaging showed thoracolumbar scoliosis* (Figs. 7.6 and 7.14) *and a lipomyelomeningocele extending between T10 and L1. The filum terminale terminated at S2 level. The patient underwent total T9, T10, and S1 laminectomy (the condition of the bone was not suitable for laminoplasty) and repair of the lipomyelomeningocele* (Fig. 7.15)*; then the TC was released at S2. She was discharged after 14 days with no improvement in her neurological scoring system. After an anesthesiologist consultation, she was planned to undergo correction for her scoliosis but after a delay of 1 year.*

Standard Management of Adult OSD

Almost all authors recommend surgery as soon as neurological symptoms appear [1, 8, 10, 13, 17, 21, 22]. However, a few have recommended surgery for those with progressive neurological symptoms [6]. We described the standard management protocol that we use to treat adult TC in previous paper [10]. Although the aim of

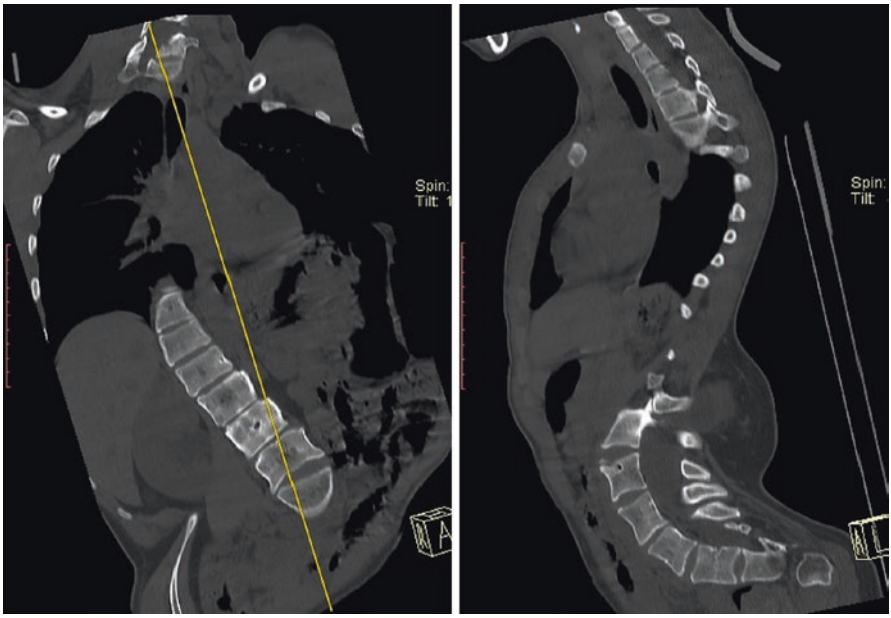

Fig. 7.14 CT of Case Study 4 showing right curved thoracolumbar scoliosis. Right side: sagittal CT. Left side: coronal CT

the initial approach of surgical intervention is to deal with the pathological conditions that cause the symptoms in symptomatic OSD patients, the surgical management of asymptomatic OSD remains controversial. Therefore, patients who present with suspicious symptoms (back pain, leg pain, and/or urinary-fecal incontinence) (Table 7.2) associated with any malformation or structural lesion such as lipomyelomeningocele, lipomeningocele, dermal sinus tract, cutaneous stigmata (hypertrichosis), scoliosis, or another system malformation (e.g., congenital heart diseases, congenital kidney diseases, or genetic syndromes) (Tables 7.1) have to undergo detailed neurological and physical examination followed by craniospinal MRIs. If any findings support OSD, the patients must undergo a urodynamic test. If all investigations lead us to diagnose the patient as symptomatic OSD, the neurosurgeons have to explain the risks, complications, and benefits of surgical intervention to the patients and their families in order to help them decide about the operative option.

If both the physicians and the patient's family opt for surgery, neurophysiological monitoring and laminoplasty rather than laminectomy have to be applied. Intraoperative surgical strategies depend on additional pathological entities associated with OSD. Klekamp recommended a complete resection, including the capsules in hamartomas (i.e., lipomas, dermoid cysts, epidermoid cysts, and neurenteric cysts), and using artificial materials for duraplasty [6]. In our series, eight adult OSD patients had lipomas, but the lipomas were resectioned in only three of those eight. One patient had recurrence after 6 years, even after complete resection of the lipoma with its capsule. To avoid serious complications and re-tethering, the lipoma

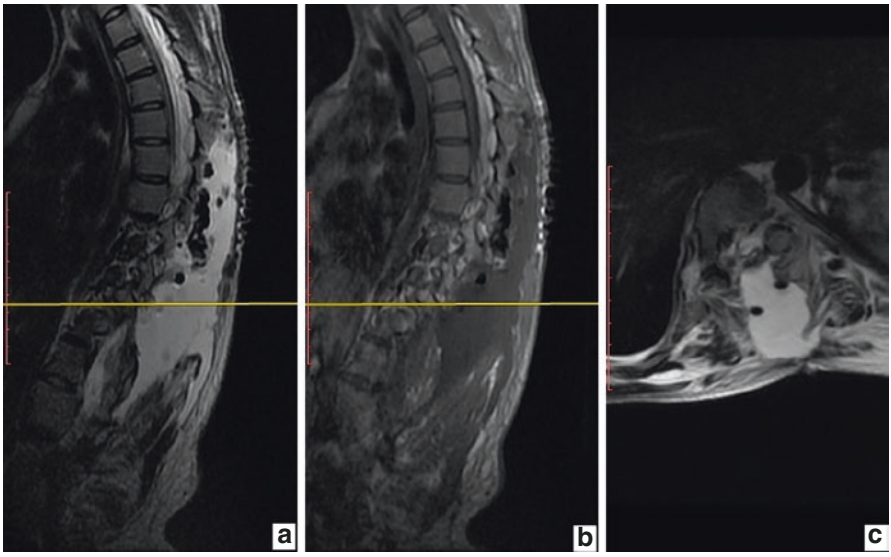

Fig. 7.15 Early postoperative MRI of Case Study 4 demonstrating reconstruction of thecal sac. (**a**) T2-weighted sagittal MRI; (**b**) T1-weighted sagittal MRI; (**c**) T2-weighted axial MRI: *yellow lines in* (**a**, **b**) show the cross-section at T10–T11 level that axial MRI shows in (**c**)

was left without resection after intraoperative evaluation showed that it did not press on nerve roots or the dural sac. However, asymptomatic patients have an increased risk of developing further neurological deterioration. Close patient follow-up and timely treatment for local pathologies after changes in urodynamic or manual motor testing are detected can protect patients from new deficits.

Adult OSD patients are less likely to show neurological deterioration because there has already been rapid spinal column growth in a spinal cord that is tethered caudally. Four of our patients did not undergo TC release; only bony septum resection had been applied. Two of those four also underwent cystectomy (Case Studies 1 and 3). The guide here is the consistency of clinical presentation and neurological examination with the urodynamic study. In these four cases, the presenting symptom was pain, while the urodynamic tests showed normocompliant normotonic bladder function with less than 50 ml postvoid residual urine (normal). Therefore, bony septum resection sufficed to resolve their complaints, rather than an untethering procedure that could result in new neurosurgical deficits. Thus, our management does not agree with the literature, in which most authors suggest that TC release is a necessary intervention in adult TC patients [6, 8, 13, 17].

Surgical Procedure

Under general anesthesia and using intraoperative neurophysiological monitoring (IONM), the patients are positioned prone using a supporting roll on each side. A paramedian vertical midline incision is made between the superior and

inferior laminas detected via MRI (e.g., if the conus medullaris is at L5 level, the incision would be extended between L4 and S1). The paraspinal muscles are dissected. If the aim is to perform partial or total (complete) laminectomy, the dissection is unilateral; if the surgeons plan a laminoplasty, the dissection is bilateral.

Hemilaminectomy, laminectomy, or laminotomy is completed (in cases of spina bifida occulta, defective laminotomy is used). If the purpose is laminoplasty, bilateral laminotomy is performed using high-speed drills or Kerrison rongeurs. Next, the ligamentum flavum and the adipose tissue are removed. The spinal cord can continue to the S1 or S2 levels by giving some sacral rootlets. Laminectomy or laminotomy should be performed up to this level. The operative microscope is brought in over the operation field. The thecal sac should be opened in the midline and tacked up bilaterally using strong sutures.

After all nerve roots, filum terminale, and arachnoid bands have been exposed, the neurosurgeons select the filum terminale using the microscope (generally senior neurosurgeons select it by its suspected structure) and IONM. Under the microscope, the filum terminale appears darker than the nerve rootlets. This darker color is related to its fibrovascular tag structure that contains a large vessel, which becomes smaller through thecal sac [7, 15, 18] (Fig. 7.16). However, this vessel is not a reliable landmark for the filum terminale since similar vessels can be found on the rootlets, and sometimes no vessel can be seen on the filum terminale [1, 10]. The use of the IONM probe is recommended to check whether the tissue is neural. This helps to avoid cutting one of the rootlets instead of the filum terminale to be tethered. The rootlets are retracted laterally, and the filum terminale is coagulated and cut after it is identified. All connective tissues attached to the caudal part of the spinal cord and conus medullaris should be released. After hemostasis using physiological saline, duraplasty is performed using 5.0 absorbable sutures (Fig. 7.13). To avoid a CSF fistula after tight closure of the dura, the surgeons use Fibrin Sealant Products. If BS or FB is present, it should be resected first, before the untethering

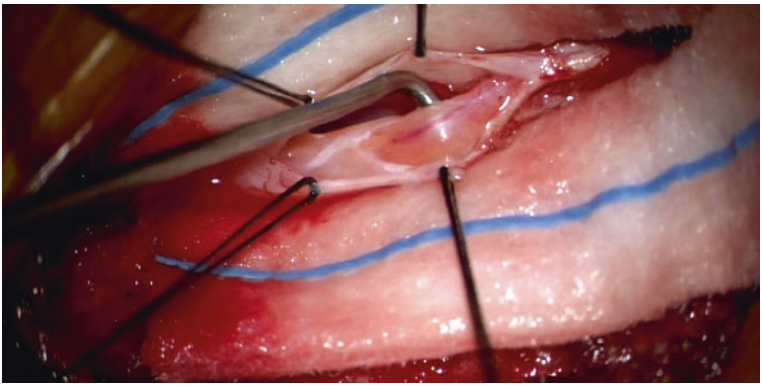

Fig. 7.16 Intraoperative photo shows TC at S2 level before untethering procedure. Note that the darker color of the terminal filum is related to its fibrovascular tag structure containing a large vessel, which becomes smaller through the thecal sac. Note the operation field is kept clean, and the CSF circulation between neural elements preserved using paddy cottons (Case Study 5)

procedure. In cases of dermal sinus, the tracts can be attached to the thecal sac. Therefore, these structures should also be removed and duraplasty should be done if necessary.

In cases of lipoma, cyst, or other hamartomas that press on the nerve rootlets and narrow the thecal sac, the hamartomas should be removed too. To avoid serious complications and prevent re-tethering, lipomas should not be removed aggressively. This decision should be taken after intraoperative evaluation, keeping the operation field clean and preserving CSF circulation between the neural elements.

Scoliosis Associated with Adult OSD

Scoliosis is defined as a lateral curvature of the spine of at least 10° with vertebral rotation. The most common type of scoliosis in the pediatric and young adult populations is idiopathic. After skeletal maturity is reached, a patient with adolescent idiopathic scoliosis is defined as having adult idiopathic scoliosis. Such patients have had scoliosis while growing into adulthood. Typically, there is a slow increase (about 0.5–2° per year) in the lateral curvature. The scoliosis associated with adult OSD generally coexists with type II SCM, has a single big curvature, and affects the thoracic and thoracolumbar spine [1, 10]. Such scoliosis is thought to be secondary to the OSD itself. It is essential to assess all scoliosis patients fully and perform craniospinal MRI before planning surgery to determine whether there is any co-malformation or OSD.

Symptoms

Shoulder asymmetry, a rib hump, or a prominence of the lower back on the side of the lateral curvature is the most physical symptoms of scoliosis. Both types of adult scoliosis can progress over time. Curves that reach 50° or more can progress more rapidly than those that are less than 50°. Neurological symptoms can include back pain, especially in adults with large curvatures, and shortness of breath with activity if the curvature in the thoracic spine exceeds 80°. Although adult scoliosis alone rarely causes paralysis or other severe neurological problems, it can be associated with OSDs such as TC or SCM, which can cause nerve irritation, leg pain, muscular weakness, and sphincter dysfunction. In our experience, two out of eight scoliosis patients presented because of their humps. Both patients were female. One of them had hemiparalysis (Case Study 4).

Diagnostic Work-Up

Scoliosis can first be recognized clinically with a physical examination. Neurological examination is mandatory for full assessment of the patient. Plain and scoliosis radiography (full-length, whole spine X-rays need to be performed) is necessary to

determine the magnitude and type of scoliosis fully. For a proper scoliosis assessment, lateral bending X-rays are used to assess the rigidity of the scoliosis. In our experience, 8 out of 31 adult OSD patients (25.8%) presented to us with scoliosis. Therefore, MRI and three-dimensional CT imaging are needed if there is OSD in a pediatric or young adult patient.

Treatment and Follow-Up

The treatment of adult scoliosis associated with OSD is very individualized and is based on the specific symptoms and age of the patient. Many adult patients with scoliosis have very minor symptoms, diagnosed incidentally, and they live with it without treatment. Patients with predominant symptoms of moderate back and leg pain are typically treated conservatively. Physical therapy exercises, swimming, and sometimes bracing can help to reduce pain intensity. Patients with severe back and leg pain can benefit from steroid injections to help relieve the leg pain. If the scoliosis curvature measures more than 50° or the patient asks to have his/her hump treated for cosmetic reasons, surgical correction can be useful. Decompressive surgery, fusion procedure, and osteotomies are the most commonly used surgical approaches. The aim of surgical intervention is to remove pressure on the nerves and spinal cord and to maintain stabilization and obtain sagittal balance of the spine. Thus, surgery stops the scoliosis from progressing. The length of the fusion, or the number of spine levels included, depends on the age of the patient, the type of scoliosis, and the spinal area involved. IONM and an expert spine surgeon team are essential for precluding serious complications. Early postoperative lung X-rays are essential for identifying lung complications.

Follow-up is mandatory after scoliosis surgery. It is important to have an adult scoliosis specialist monitor the curvature over time. These curvatures can worsen owing to disc degeneration, which can happen in elderly patients. This can also cause sagittal imbalance because it makes the patient lean progressively further forward. In severe cases, arthritis in the spine facets can lead to bone spurs, local back pain due to stiffness of the back, radiating leg pain, and numbness down the legs from pinched nerves.

Case Study 5 *An 18-year-old female was referred to us from another country with a hump in her back. Her mother said she had had spinal malformation since birth. Her hump was minimal up to the age of 12. Her neurological examination was intact. Full-spine X-ray showed left curved thoracolumbar scoliosis (T2–L3) of 105°* (Fig. 7.17a). *MRI and CT imaging showed left curved thoracolumbar scoliosis extending between T2 and L3* (Fig. 7.18a). *The filum terminale terminated at S2 level* (Figs. 7.18b, c). *The patient underwent total S2 laminectomy, and then the TC was untethered at the S2 level* (Fig. 7.16). *After 2 days, posterior instrumentation was performed between the T3 and L2 vertebral bodies, followed by a right T8 hemicorporectomy* (Fig. 7.17b). *The follow-up X-rays demonstrated a curve*

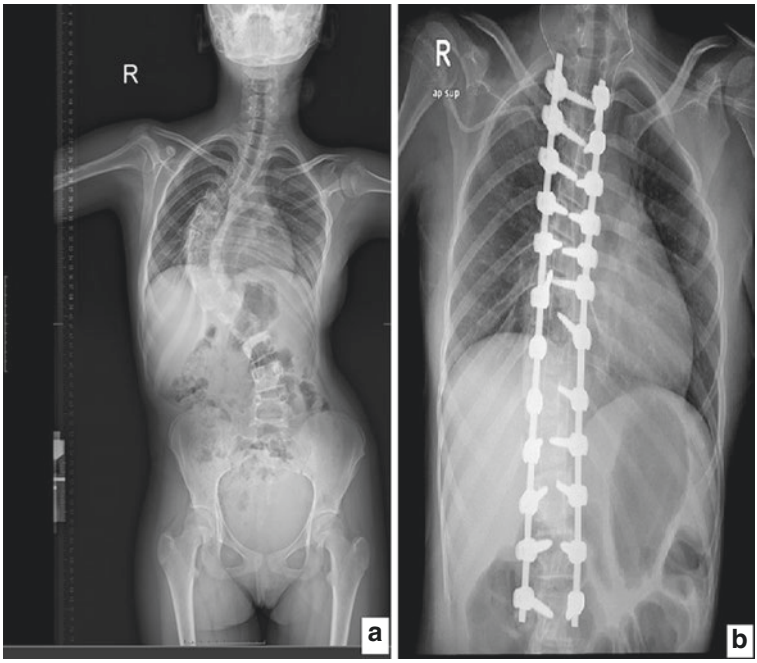

Fig. 7.17 An 18-year-old female patient presented with a hump in her back. Plain full-spine X-ray of Case Study 5: (**a**) preoperative X-rays showed left curved thoracolumbar scoliosis of 105°; (**b**) early postoperative X-rays

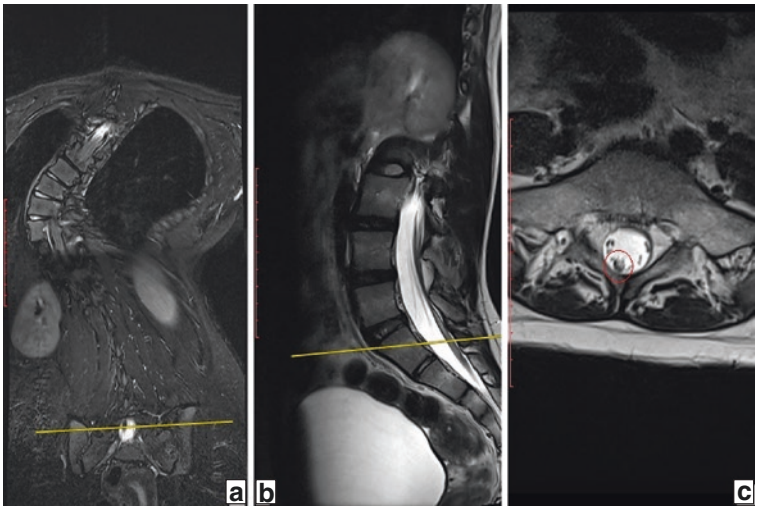

Fig. 7.18 Preoperative MRI of Case Study 5: (**a**) STIR coronal MRI demonstrated left curved scoliosis; (**b**) T2-weighted sagittal thoracolumbar MRI demonstrated cyst was excised totally; (**c**) T2-weighted axial lumbar MRI showed axial cross-sectional S2 level – note TC at S2 level; *yellow lines in* (**a**, **b**) show the cross-section at S2 level that axial MRI shows in (**c**)

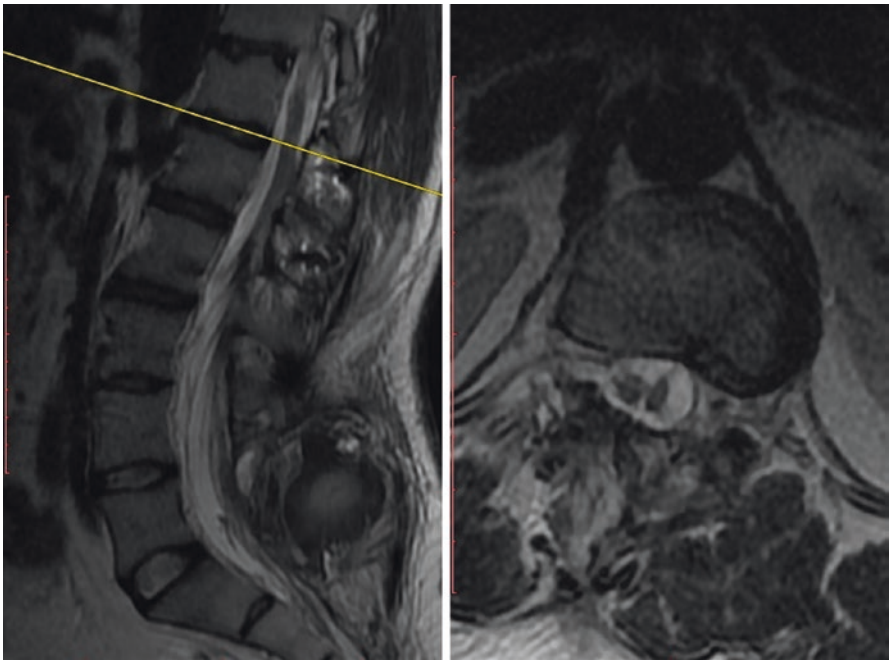

Fig. 7.19 A 31-year-old male presented with low back and left leg pain for 3 years and muscular weakness for 3 months. Early postoperative T2-weighted MRI demonstrated resection of FB at T12-L1 level. Left side: sagittal MRI; *yellow line* shows the cross-sectional T12-L1 level that axial MRI shows on the left side. Right side, axial MRI demonstrated diastematomyelia postoperatively (Case Study 6)

correction to 18 and a balanced spine. The patient was discharged after 7 days without complications. On her postoperative 15th-month doctor visit, she was doing well.

Case Study 6 *A 31-year-old male presented with low back and left leg pain for 3 years and muscular weakness for 3 months. The patient smoked and was on medication for hypertension. His neurological examination was intact except for weakness in his left leg distal muscles group of 2/5, left L2–L5 and S1 dermatomal hypoesthesia, unsteady gait, increased response of deep tendon reflexes in the left leg, and atrophy in his left leg (right and left pretibial circumferences were 28.1 and 24.2 cm, respectively). MRI showed diastematomyelia at T12-L1, and split cord malformation as a fibrous band at L3 level was apparent* (Fig. 7.19)*. The filum terminale terminated at L5 level. CT showed a left curved thoracic scoliosis of 35°* (Fig. 7.20)*. Urodynamic study showed normocompliance normotonic bladder function. The patient underwent FB resection and duraplasty using total T12-L1 laminoplasty* via *mini screws plaque* (Fig. 7.21)*, followed by release of the TC at L5 level using total L5 laminectomy* (Fig. 7.22)*. The patient's pain decreased but neurological status did not improve. He was discharged after 10 days without complications and was referred to the physiotherapy department.*

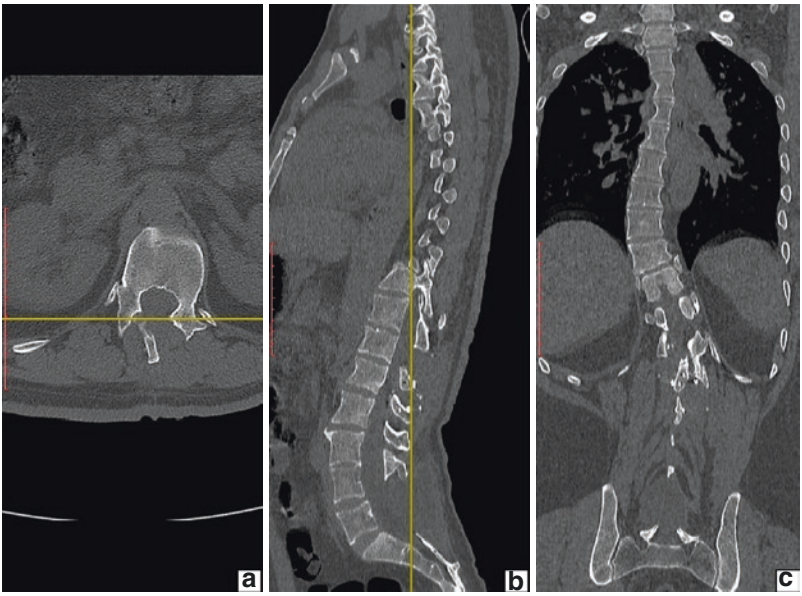

Fig. 7.20 CT of Case Study 6 showing thoracic scoliosis: (**a**) axial CT; (**b**) sagittal CT; (**c**) coronal CT

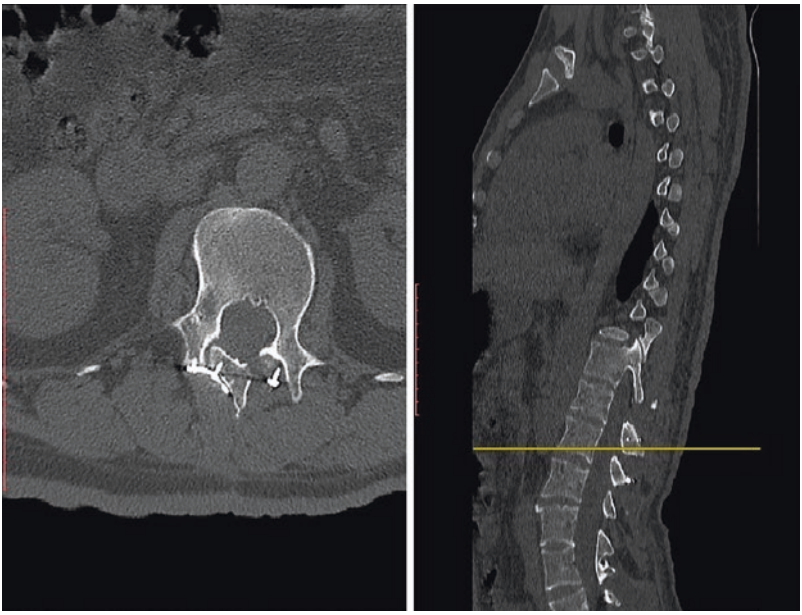

Fig. 7.21 Postoperative CT of Case Study 6 showing L1 laminoplasty using mini screws plaque. Left side: axial CT. Right side, sagittal CT

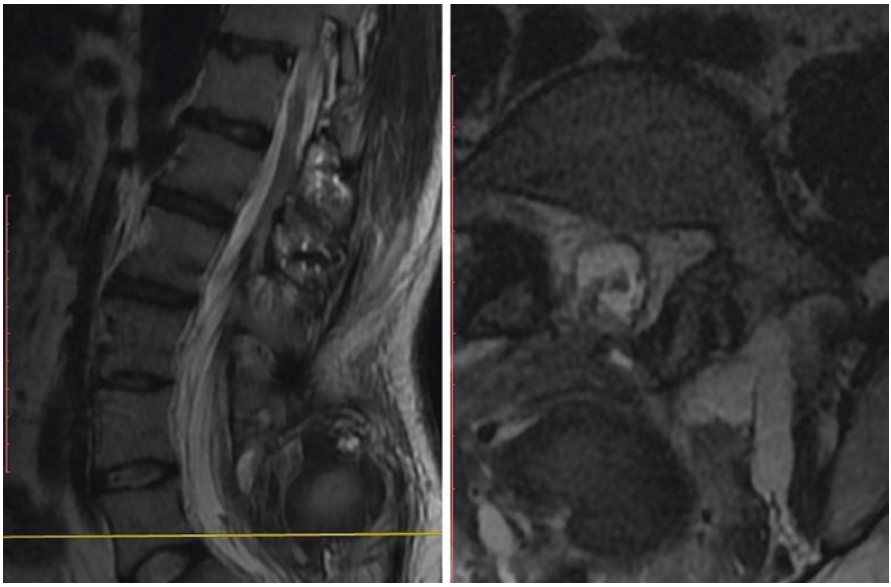

Fig. 7.22 Early postoperative T2-weighted MRI of Case Study 6 showed releasing TC at L5 level. Left side: sagittal MRI; *yellow line* shows the cross-sectional L5 level that axial MRI shows on the left side. Right side: axial MRI

Surgical Outcomes of Adult OSD Patients

Early surgical intervention after increasing intensity of pain or severity of complaints gave good results; good recovery was seen in 64.5% and improvement in 29.0% of our patients. Only two patients had worsened neurological deficits. Our good surgical outcomes were related to the full assessment of each patient separately. Those who were diagnosed incidentally with TC after moderate pain were closely followed up, and when their complaints started to be symptomatic and urological complaints were added to their clinical pictures, urodynamic studies were re-performed, and then a decision was made for surgical intervention.

Iskandar et al. [17] reported that untethering improved 22 of 27 patients (81.5%) presenting with pain, 13 of 27 (48.1%) with motor or sensory dysfunction, and 11 of 18 (61.1%) with bowel and bladder disturbances. Sofuoglu et al. [10] reported that TC release and/or BS resection in their patients improved and eliminated pain in 15.8% (3 out of 19 patients) and 84.6% (16 out of 19), respectively. Muscular weakness recovered in 8 of their 12 patients (66.7%), was unchanged in 2, and worsened and improved in 1 patient each. However, sensory disturbance remained unchanged in 50% (four out of eight patients) in their series. Bladder and bowel dysfunction improved, recovered, and remained unchanged in 50% (6 out of 12 patients), 25%, and 25%, respectively. These surgical outcomes are better than those

reported by Lee et al. [8], who found that surgical intervention improved back and leg pain in 78% and 83% of patients, respectively. Motor weakness stabilized or improved in only 27% and 64% of their patients, respectively. Sensory deficits remained unchanged in 50%. Urological abnormalities improved in 50% of patients undergoing untethering and remained stable in 45%.

Surgical outcomes of adult OSD patients are rated as recovered, unchanged, or worsened. Unless the surgical intervention leads to full recovery or resolution of the major symptoms (leg and/or back pain, motor weakness, sphincter dysfunction, or gait ataxia) that affect the patient's quality of life, patient satisfaction and quality of life continue to be poor. Therefore, we divide the surgical outcomes into two major groups. The first is the "fully recovered group" comprising patients who have good clinical outcomes with resolution of their major symptoms. The second is the "others group," which includes all cases with at least one major symptom unresolved. We investigate the factors that could have affected the outcomes in our 31 adult OSD patients.

Gender and Age

The mean age of our adult OSD patients was 32.1 ± 11.8 (18–68) years. At their final follow-up, after 62.9 months on average, 64.5% had good clinical outcomes. The 20 recovered patients comprised 13 females and 7 males. The gender factor was not statistically significant (OR 0.45, $p = 0.25$). The mean age of the recovered group was 31.2 ± 10.2 (20–61) years, while that of the "others group" was 33.5 ± 11.3 (18–68) years. Although the recovered group was younger on average, the age factor was not statistically significant (OR 0.93, $p = 0.88$).

Long-Term Symptoms and Neurological Examination on Presentation

The interval between the initial symptom and the time of surgical intervention in our sample ranged between 4 months and 25 years with an average of 5.2 years. Bladder dysfunction when associated with muscular weakness (OR 7.0, $p = 0.014$) and long-term (i.e., more than 6 months) symptoms (OR 24.5, $p = 0.0001$) are independent risk factors leading to poor, minimally improved, or almost unchanged surgical outcomes even after rehabilitation programs. Therefore, we recommend early surgical intervention in symptomatic patients irrespective of the fact that most OSD or TC cases diagnosed in adults are asymptomatic. During the last 12 years, our team diagnosed 116 adult patients with OSD after incidental permanent or severe pain in the back and/or leg or after serious urological complaints. Only 31 adult patients (26.7%) who were diagnosed as symptomatic OSD were treated surgically. Klekamp reported that only 50.8% of adult patients with TC underwent an untethering procedure [6]. Asymptomatic TC in our sample was identified in 85 patients (73.3%).

Patients have to undergo full neurological examinations, especially those who experience low back and leg pain associated with urination complaints and those with malformations associated with TC (Table 7.2). Surgical intervention is recommended in children and adolescents to reduce the expected risk of further neurological deficits [10].

Associated Malformations

Three patients (9.7%) in our operated 31 adult OSD were free of other malformations associated with TC (Table 7.1). In our experience, seven out of eight patients with SCM were treated by BS or FB resection. Only four of those seven needed a subsequent untethering procedure to relieve their pain or other complaints. In the remaining three patients, the untethering procedure was not applied, so new neurological deficits were precluded. Out of eight patients with lipoma, only two were treated by removal of the lipoma. A third patient was treated by cystectomy. Four out of five patients who presented with dermal sinus tract were treated by resection and surgical repair of the skin. Except for two young adult female patients with scoliosis (who wanted the operation for cosmetic reasons), patients with scoliosis and syringohydromyelia did not need additional surgical intervention, but 38% of our child TCS patients who presented with the same malformations underwent additional surgery to treat their complaints [10]. Surgical outcomes in cases without lipomas have better recovery chances than those with lipomas (OR 2.4, $p = 0.001$). Aggressive surgical treatment of lipoma was the reason behind the only recurrence case 6 years later. Lipoma was associated with motor weakness, atrophy, or bladder dysfunction, but only with trend-level significance (OR 1.49, $p = 0.09$).

Surgical Approaches

IONM and laminoplasty have been integral to surgery, especially in recent years. IONM is useful for distinguishing functional from nonfunctional nerve roots. Thus, neurosurgeons can reduce the serious complications that could result from surgical intervention in adult OSD cases. Laminoplasty reduces the adhesions that could facilitate recurrence of TCS in adults; even our recurrent patient underwent laminoplasty, but his recurrence was thought to be related to the aggressive removal of the lipoma.

Comparing laminoplasty, hemilaminectomy, and laminectomy in our sample, the authors found that laminoplasty leads to a mean hospital stay of 3.9 ± 2.2 (2–8) days, which is shorter than for the hemilaminectomy and laminectomy approaches, which lead to mean hospital stays of 4.0 ± 2.2 (2–7) and 6.4 ± 3.3 (3–12) days, respectively. However, the difference is not statistically significant ($p = 0.57$ and $p = 0.29$, respectively). None of the three approaches is superior to the others in regard to surgery-related complications.

A multivariate regression model showed that compared to laminoplasty (OR 2.05, $p = 0.047$) and hemilaminectomy (OR 1.875, $p = 0.049$), laminectomy is independent of other risk factors associated with poor or marginally improved (almost unchanged) surgical outcomes. This statistically significant difference could be related to IONM, not to the approach itself.

In cases of lipoma, cyst, or other hamartomas that press on the nerve rootlets and cause narrowing of the thecal sac, the hamartomas should be removed too. To avoid serious complications and to prevent re-tethering, lipomas should not be removed aggressively. This decision should be taken after intraoperative evaluation. The operation field should be kept clean, and the CSF circulation between the neural elements should be preserved.

In the adult population, the rate of re-tethering is reportedly as high as 29% [5, 6, 17, 19, 20, 24]. Re-tethering developed in one of our male patients 6 years postoperation, so the re-tethering rate in our patients was only 3.2%. This patient underwent an untethering procedure and partial surgical resection of his lipoma. His case shows that laminoplasty is effective in protecting the thecal sac and nerve roots from fibrosis and granulation tissues.

Pre- and Postoperative Urodynamic Studies

The urodynamic test has value in predicting most of the future deteriorations in adult OSD patients. Adults diagnosed incidentally with OSD after moderate pain were followed up closely. When their complaints started to become symptomatic and urological complaints were added to their clinical pictures, urodynamic studies were re-performed, and the surgical intervention decision was taken.

We recommend surgery for adult OSD patients whose urodynamic test shows an overactive detrusor muscle. Postoperative urodynamic tests show no improvement in those patients. The long-term symptoms can be held responsible for this. On the other hand, when the urodynamic tests showed postvoid residual urine >100 ml, especially in patients with short-term (under 6 months) symptoms, postoperative urodynamic tests showed improvement in all 12 patients (either normal or close to normal residual urine: 50–100 ml) ($p = 0.0001$).

Complications of Adult OSD

Despite the good results obtained in almost all surgical interventions for symptomatic OSD in adults, tethered cord releasing is a complex procedure and has serious complications. Therefore, it is suggested that surgery be planned according to the dominant symptoms, with full neurological examination, craniospinal MR imaging, and urodynamic tests.

Over the 12-year period of our experience, surgery-related complications included three out of 31 (9.7%) patients suffering CSF leakages, three (9.7%) suffering surgical site infections (SSI), and one (3.2%) suffering a late pseudomeningocele. This

pseudomeningocele developed in a female patient 4 years after untethering surgery. All of these patients were successfully treated either conservatively or surgically. Two of our 31 patients (6.5%) complained of worsening muscular weakness. Iskandar et al. [17] reported that one of their 34 patients (2.9%) suffered CSF leakage, 5 (14.7%) suffered pseudomeningocele, 2 (5.9%) complained of worsening bladder dysfunction, 4 (11.8%) experienced persistent pain, and 1 (2.9%) complained of worsening pain postoperatively.

In the adult population, the rate of re-tethering is reportedly as high as 29% [5, 6, 17, 20, 24]. Usually recurrent TCS can lead to the same significant complaints seen in patients before primary surgery. Re-tethering was observed in one (3.2%) of our patients, who underwent an untethering procedure and complete resection of his lipoma surgically, and then improved. The patient was doing well on his postoperative 38th-month doctor visit. In this case, the authors noticed that laminoplasty was effective for protecting the thecal sac and nerve roots from fibrosis and granulation tissues. Solmaz et al. [18] reported a high re-tethering rate of 24.5% among children with TC.

To avoid serious complications, neurosurgeons have to study the craniospinal MRI carefully. If necessary, CT must be performed to investigate the bone structures. IONM and laminoplasty are also needed. To prevent re-tethering, lipomas should not be removed aggressively; the operation field should be kept clean, and CSF circulation between the neural elements should be preserved. Fibrin Sealant Products can be required for avoiding CSF fistula formation after tight closure of the dura.

Follow-Up of Adult OSD Cases

Patients with tolerable pain, which was seen in all of the adult patients with OSD in our series, were treated conservatively, with close follow-up (3-month periods) to preclude permanent new neurological deficits. Operated adult TCS patients were subjected to full neurological examinations on the 1st-, 3rd-, 6th-, 12th-, and 24th-month control visits. Subsequently, each patient was called every 2 years if he/she had no new complaint. The patients must be evaluated pre- and postoperatively according to a neurological scoring system [10] (Table 7.4). If the patient experiences the same symptoms as those presenting before surgery, lumbar MRI has to be performed.

Conclusions

OSDs are congenital deteriorations that can lead to serious complaints. Despite the good results reported after surgical interventions for symptomatic OSD in adults, surgical intervention such as tethered cord releasing is a complex procedure and has serious complications. Therefore, it is suggested that surgery be planned according to the dominant symptoms, with full neurological examination, craniospinal

imaging, and urodynamic tests. Laminoplasty (or hemilaminectomy), short-term (less than 6 months) symptoms, patients without lipomas, and presentation with moderate or mild symptoms seem to be reliable predictors for good surgical outcomes. Urodynamic study can be used as a predictive tool for diagnosing TCS in asymptomatic adult patients, and it could be a good predictor for disease prognosis.

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The Tethered Cord Syndrome and Its Occult Form

8

Bermans J. Iskandar and Steve C. Amaefuna

Congenital Spinal Defects Cause Stretching/Tethering of the Spinal Cord

A clinical description of the spinal cord under undue tension first appeared in the medical literature in 1857. Johnson reported a pediatric patient with a "fatty tumor of the sacrum…connected with the spinal membranes" [1]. Eighteen years later, Jones (1891) described the first surgical intervention on the spine to relieve pressure on the cauda equina [2]. Another few passed before Fuchs (1910) hypothesized that the intermittent incontinence seen in patients with myelomeningocele was due to increased tension on the distal spinal cord during flexion [3]. Lichtenstein was the first to employ the term "spinal dysraphism," and although he helped further the concept of cord dysfunction secondary to tethering lesions, his hypothesis linking this to the Chiari malformation was ultimately not accepted [4, 5]. Subsequent articles continued to expand on distal spinal cord disorders such as sacral lipomas and occult spinal dysraphism (OSD), although they made little reference to any tethering effect, and instead attributed neurological deficits to lipomatous infiltration or congenital neuronal dysgenesis [6, 7].

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The Tethered Cord Syndrome Is the Clinical Manifestation of Such Stretching

Surprisingly, the filum terminale was not mentioned in the context of a tethered spinal cord until Garceau's description in 1953 of "filum terminale syndrome" involving three patients demonstrating clinical improvement following lumbar laminectomy and the severing of a thick, tight filum terminale [8]. Garceau's findings implicating a tight filum terminale in spinal cord tension-induced neurological dysfunction were later supported by the work by Jones and Love and by James and Lassman [9, 10].

Evidence of Tethered Cord Syndrome (TCS)

Anatomical

Anatomical correlations of the clinical manifestations of a tethered conus were first introduced by Fitz and Hardwood in 1975 with their classification of a "conus tip below the L2-3 interspace in a child older than five years" and a "filum measuring greater than two mm on myelography" as abnormal [11] (Fig. 8.1). Subsequently, there was no concrete definition of the syndrome until the 1976 surgical series by Hoffman et al., describing 31 patients with symptomatic improvement following

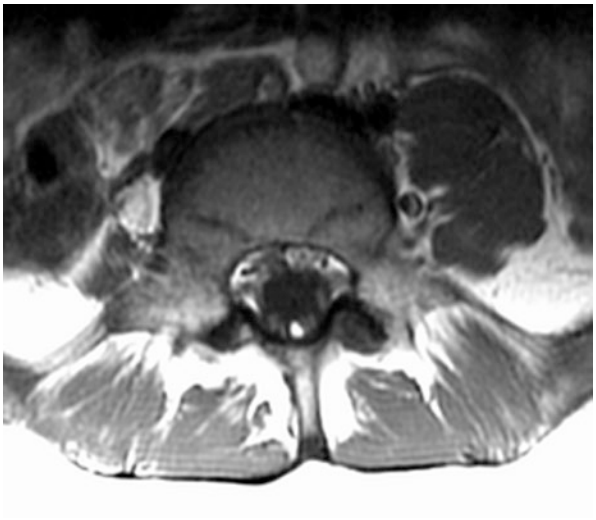

Fig. 8.1 An 11-year-old female who remained unable to walk until 4 years of age. She presented with chronic progressive back pain, progressive lower extremity weakness, and progressive bladder incontinence. The figure shows a T1-weighted axial image of the mid-lumbar spine depicting a thick and fatty filum terminale. The conus medullaris is low lying, terminating at the mid-L3 vertebral level. This case represents a typical symptomatic TCS patient

sectioning of a thickened, tight filum. This was the first clinical description of "tethered cord syndrome" (TCS) and helped establish a "low conus medullaris and a thickened filum terminale measuring 2 mm or more in diameter" as diagnostic criteria [12–16].

Physiological/Experimental

Despite an impressive body of clinical evidence describing the associated motor and sensory changes, there remained a relative lack of mechanistic understanding of the presumed neuronal dysfunction in TCS. In 1981, Yamada et al. provided the most compelling evidence for a possible mechanism [17]. Defining TCS as a "stretch-induced functional disorder of the lumbosacral spinal cord," they used human and feline experimental models to establish that caudal traction on the distal spinal cord results in diminished blood flow and a semi-reversible impairment in oxidative metabolism that manifests as neurological deficits. Both the degree and reversibility of cord dysfunction depend on the magnitude and duration of cord traction. The authors also concluded that chronic tension leads to pre-loading of the distal spinal cord, allowing severe and permanent injury to occur as a result of even minor additional stretching [18–20]. Kocak et al. reported similar findings using a guinea pig model [21].

The Basic TCS Anomaly Is the Tight Filum Terminale

Low-Lying Conus Medullaris

Yamada [19] summarized his findings in a description of TCS that included updated diagnostic imaging criteria in the form of (1) a thick filum terminale (>2 mm in diameter) and/or a structural decrease in viscoelasticity (fibroadipose tissue, etc.), (2) an elongated spinal cord, and, uniquely, (3) posterior displacement of the conus medullaris with the filum terminale pressed against the thecal sac. Although the level of the conus tip was deemed nonessential in this summary, this diagnostic criterion has obviously persisted [13, 19, 22].

Classic TCS Surgical Series

This new pathophysiological evidence behind TCS coincided with an effort at better establishing the surgical experience associated with cord untethering. In one of the first relevant surgical series on TCS, Pang et al. reported on 23 adult patients [22]. All 23 met TCS criteria on the basis of a conus tip "below the lower border of the L2 vertebral body" and a spectrum of preoperative signs and symptoms that included pain, sensorimotor deficits, urinary bladder dysfunction, bowel dysfunction, and cutaneous manifestations. The authors reported postoperative improvement in pain

and sensorimotor deficits in 83.3% and 86.7% of patients, respectively, with modest improvement recorded for bladder dysfunction (38.5%) but no improvement in bowel dysfunction. This pattern has been replicated, with more recent reports demonstrating the successful stabilization of neurological decline and a consistently high rate of postoperative pain resolution, both within the 80–100% range. Rates of improvement following untethering have been more variable regarding other common preoperative complaints such as urological dysfunction [19, 23–26]. While other literature has confirmed Pang's findings of rates of improvement as high as 87%, several other reports and reviews show rates of improvement as low as 16% [22, 25, 27–31]. Admittedly, much of this variability is due to differences in the way outcomes are measured.

TCS from Other Lumbar Spinal Anomalies

In addition to breaking ground on the pathophysiology behind TCS, Yamada et al. also broadened the clinical definition of TCS by correlating the stretch-induced cord dysfunction seen in this condition with similar neurological changes in patients with other distal cord anomalies such as myelomeningocele, lipomyelomeningocele, and other forms of spinal dysraphism [17]. These observations were published within a year of the similar conclusions by James and Lassman in their classic monograph "Spina Bifida Occulta," which implicated spinal cord tethering in a variety of dysraphic lesions including lipomyelomeningocele, diastematomyelia, meningocele manqué, and dermal sinus tract. Nevertheless, as more and more cases appeared in the literature, the trend was clearly toward a more inclusive etiological differential for TCS secondary to some form of cord tethering.

Emergence of OTCS

TCS in Patients with Normal Conus and Filum Anatomy (Occult TCS)

Hoffman et al. deepened this diagnostic spectrum with a second surgical series demonstrating clinical improvement in patients who presented with the characteristic neurological findings of TCS together with myelographic abnormalities. However, this subsequent surgical description included a subset of patients whose sole anatomical finding was a "tight filum," defined only by its tendency to "spring apart when transected" intraoperatively. Despite a normally positioned conus and non-thick filum terminale, TCS was diagnosed in these patients, and surgery was performed given only a combination of "classical" signs and symptoms and the presence of bony spina bifida occulta [32–34]. This series set the stage for the diagnosis of TCS in the absence of a low-lying conus and eventually an array of controversial papers on "occult tethered cord syndrome" (OTCS).

TCS with Conus in Normal Position (Warder and Oakes)

During the past two decades, a number of authors have offered evidence to support operating on patients with TCS-like symptoms with a normally positioned conus. In their retrospective series involving 13 patients with TCS "in whom the spinal cord terminated at or above the L1–L2 disc space," Warder and Oakes were the first to discuss the criteria for operating on TCS patients without a low-lying conus medullaris (Fig. 8.2). Given a history significant for incontinence and spina bifida occulta, the authors selected patients on the basis of cutaneous, neurological, and/or anatomical findings, most frequently including filar lipomas. Ten (77%) of these patients presented with neurological deficits. Lower extremity weakness, spasticity/hyperreflexia, and bladder dysfunction were the most common complaints, each occurring in four of ten (40%) patients. Bowel dysfunction was slightly less common, occurring in three of ten (30%). Cutaneous stigmata including lumbosacral

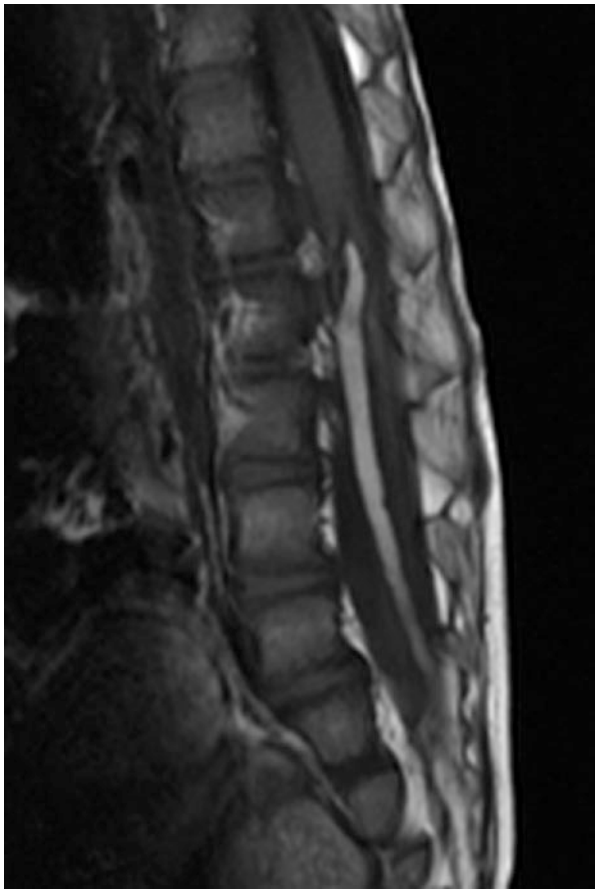

Fig. 8.2 TCS with conus in normal position. An 18-month-old female with multiple congenital abnormalities who presented with progressive scoliosis. The figure shows a T1-weighted midsagittal MR image of a very thick and fatty filum terminale with a normally positioned conus medullaris at the L1 vertebral level. The abnormal filum in this case cannot be denied, and most surgeons would choose to treat. However, the natural history and cause and effect between TCS and scoliosis can be questioned

hemangioma, lumbosacral subcutaneous lipoma, and a midline skin tag were identified in 4 of 13 (31%), 1 of 13 (8.5%), and 1 of 13 (8%) patients, respectively. Extremity abnormalities including leg length discrepancy and foot deformities were present in 3 of 13 (23%) and 2 of 13 (15%), respectively. Radiographic findings consisting primarily of bifid vertebrae were reported in 10 of 13 (77%) patients. Intradural pathologies of occult spinal dysraphism including lipoma of the filum, diastematomyelia, meningocele manqué, and syringomyelia were present in eight of ten (80%) patients. Fat in the filum terminale was confirmed "either microscopically or radiographically" in 12 of 13 patients (92%). Outcomes were based on a reassessment of presenting symptoms and their categorization as improved, unchanged, or worsened during a follow-up period of 6 months to 6 years. The authors reported "improvement or stabilization of the majority of the presenting neurological complaints" and endorsed the consideration of filum release in this population of patients [35–37]. Although they were appropriately cautious about their assertions, this article still succeeded in setting a precedent for the surgical management of TCS in patients with a normally positioned conus.

Did These Patients Have OTCS?

At the most superficial level, one must first consider the exact diagnosis in this cohort of patients. Warder et al. defined their surgical indications clearly and attempted to establish a diagnosis of TCS in all of their patients. Not surprisingly, they made sure to emphasize the presence of either cutaneous or anatomical hallmarks of occult spinal dysraphism. In the absence of a more concrete definition of OTCS and lacking any evidence to suggest otherwise, these patients all fell within the growing gray area between OTCS and classic TCS. Cautionary claims aside, a cursory analysis of this series yields room for interpretation. Foremost among the causes of irresolution is the bias inherent in relying on patient reports for outcomes data, and data indicating 20–50% prevalence of bony spina bifida occulta and a 6% incidence of fat in the filum terminale in the general population [35, 38] (Fig. 8.3). Consequently, this paper did little to dispel the mystery surrounding OTCS.

Diagnosed OTCS Surgical Series (Nazar et al.)

In stark contrast, Nazar et al. reported 32 definitive cases of "occult tethered cord syndrome" (OTCS) in their pediatric surgical series [39]. Presenting problems included severe back and/or leg pain, daytime urological problems, encopresis, or a combination of symptoms. In addition to a thorough history and physical examination, each patient was imaged via lumbar and sacral spine X-rays, lumbar MRI, and CT/myelography. Patients presenting with urological symptoms underwent pre- and postoperative urodynamic studies to assess detrusor hyperreflexia. Outcomes included a comparison of pre- and postoperative pain symptomology, the ability to return to performing a full range of physical activities, urodynamic studies when applicable,

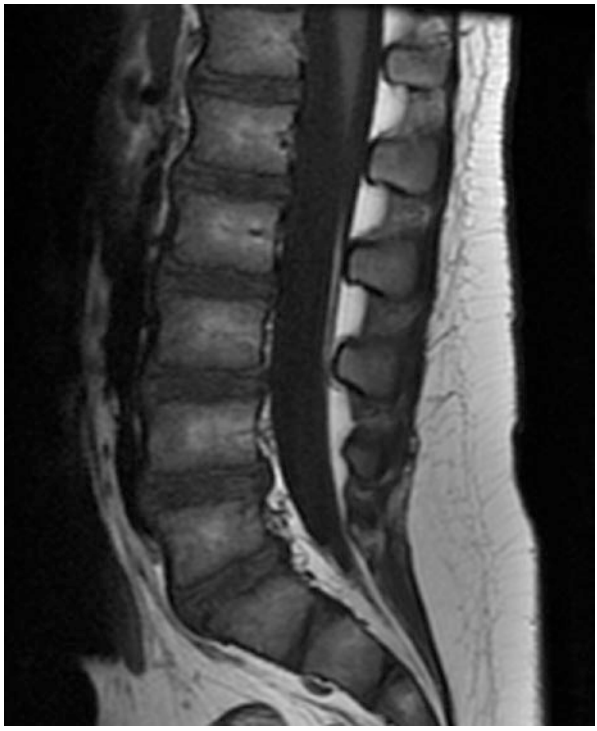

Fig. 8.3 A 6-year-old male with a symptomatic Chiari I malformation in the absence of symptoms of a tethered cord. The figure shows a T1-weighted midsagittal MR image of a thick and fatty filum terminale with a normally positioned conus medullaris at the L1 vertebral level. Should this filum be considered abnormal?

and the percentage decrease in reported urinary incontinence/frequency/urgency. Pain was the most common complaint and was present in 22 of 32 (69%) patients. Pain was the only complaint in 9 of the 32 (28%) and was associated with other symptoms in 13 (41%). Daytime urological dysfunction was present in 22 of 32 (69%) patients and was associated with pain in 10 of 32 (31%). Preoperative urodynamic studies were obtained in 20 patients and revealed small bladders, early detrusor contractions, and poor sensation in most cases. Bowel incontinence was present in 11 of 32 (34%) patients preoperatively. Physical findings other than those associated with pain were largely absent, and only 2 of 32 (6%) patients displayed cutaneous markings typically associated with spina bifida occulta in the form of a cutaneous lumbar hemangioma and lumbar hypertrichosis. Only 3 of 32 (9%) patients presented with an abnormal neurological exam in the form of absent ankle jerk in two and lower extremity weakness with an associated limp in one. MR imaging confirmed the tip of the conus medullaris above the L2 vertebral body and a lipoma-free filum terminale measuring less than 2 mm throughout its entire course in all 32 patients. Lumbar X-rays identified bony spina bifida occulta in 28 of the 32 (88%). The filum terminale was identified and sectioned intraoperatively in all 32 patients, and histological examination confirmed a normal-appearing filum without fat infiltration, scarring, or hemorrhage. During follow-up of 2–48 months, pain was relieved in 22 patients, all of whom returned to full independent activity. Daytime urinary bladder function normalized in

14 of the 22 patients (64%) and showed 50% or greater improvement with respect to a decrease in frequency/urgency/incontinence in 7 of the 22 (32%) postoperatively. Similarly, eight of nine (89%) patients demonstrated increased bladder capacity and sensation during postoperative urodynamic testing. Interestingly, only nine patients underwent urodynamic assessment postoperatively compared to 20 prior to surgery. Stool incontinence resolved in 9 of 11 patients (82%). Despite their willingness to commit to a diagnosis of OTCS, Nazar et al. largely avoided drawing conclusions from their observations in a pattern similar to Warder and Oakes, simply stating that "sectioning of a normal-appearing filum terminale appeared beneficial in the majority of patients." Although cautiously nonconclusive in practice, it became harder and harder to ignore the impact of multiple surgical series describing positive operative outcomes in patients with either OCTS or, more confusingly, a TCS-like syndrome with imaging abnormalities that, if not absent, at least did not fit the previously established "classic" criteria of TCS (Fig. 8.4).

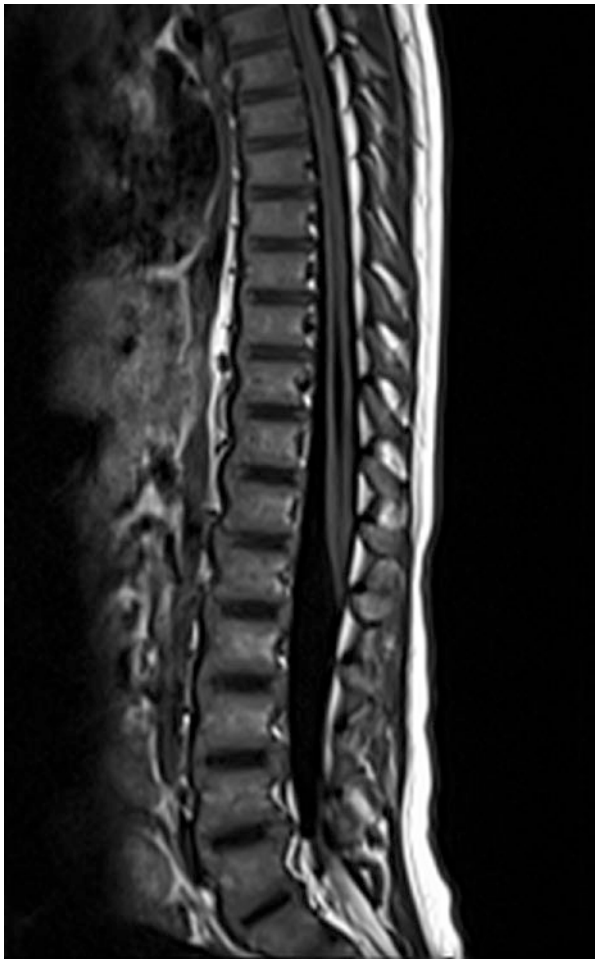

Fig. 8.4 A 4-year-old male with history of a progressive neurogenic bladder (worsening urodynamics) and lower extremity fatigue, a normal neurological examination, and a thin distal spinal cord syrinx. This is a T1-weighted midsagittal MR image showing the syrinx, as well as a posteriorly displaced conus medullaris ending at the L1 spinal level. There is no evidence of a Chiari I malformation, spinal cord tumor, or other possible etiologies of the syrinx. This case illustrates the gray zone between TCS and OTCS. The only abnormalities on this scan are the syrinx and, according to some authors, a posteriorly displaced conus

Is OTCS a Real Diagnosis?

Signs and Symptoms Occur in Normal Patients

The first issue to examine is the actual existence of OCTS. As we have discussed in some detail, much of the confusion surrounding the diagnosis lies in differing definitions. The combination of a broad spectrum of etiologies, all possibly leading to the same stretch-induced pathophysiology behind TCS, and the increasingly popular practice of surgical management in the absence of radiographic findings has left substantial room for interpretation. This is concerning, since in the context of normal imaging, many of the symptoms used to diagnose OTCS including back pain and urological dysfunction have a relatively high prevalence in otherwise healthy populations. For example, low back pain has a prevalence ranging from 24% to 58% in school-aged children between the ages of 11 and 14 years [40–42]. Similarly, urinary bladder incontinence is a problem affecting 20–40% of office visits to pediatric urologists with a prevalence rate between 11% and 20% among children in the 4–10 year age range [43–45]. Given the marked improvement in urinary incontinence reported after cord untethering, it is important to note that in most cases of pediatric urinary incontinence, the differential diagnosis list can be extensive, and there is spontaneous improvement in almost 90% [45, 46]. This raises several questions regarding both the diagnosis of OTCS and any benefit derived from filum sectioning versus time and medical management [47].

Do We Need to Operate on OTCS Patients?

Beyond the immediate symptomatic improvement described following filum sectioning, the decision to operate in the context of cord tethering is frequently predicated on a natural history for tethering lesions, occult or otherwise, that is described as both progressive and inevitable [17, 34, 48, 49]. Some recent evidence suggests that clinical deterioration is not inevitable in this patient population. In their small retrospective analysis, Steinbok et al. described 15 cases of children with refractory urinary incontinence and "possible OCTS" based on a normally positioned conus and no other visible explanation for urinary incontinence. Following discussions with families about filum sectioning as an "unproven but potentially beneficial procedure," eight chose surgery, and seven chose more conservative measures. After a mean follow-up of 3.3 years, there was no evidence of deterioration in any of the conservatively managed patients, and 29% of them showed some improvement in their symptoms [50]. This must of course be compared with the 88% of patients who showed symptomatic improvement following surgery. However, it is most concerning that much of the literature surrounding filum sectioning in OTCS lacks a benchmark for significance, yet there is a widespread disagreement about both the diagnosis and the treatment of OTCS, most physicians expressing unease about the practice [51]. Such a wide distribution in the absence of concrete data is surprising and questions our contemporary threshold for what we claim to be data-driven changes in clinical practice.

No Established Diagnostic Tests

Although a patient population exhibiting the clinical picture of TCS in the absence of lumbar cord abnormalities is possible, if not likely, the relative size of that population is unknown. Accordingly, what needs to be rigorously established is a minimum constellation of signs and symptoms warranting surgical intervention. Along these lines, some have proposed additional noninvasive testing to identify patients with suspected OTCS given the diagnostic limits of urodynamic testing. One example involves the use of dynamic structural imaging of the spine via ultrasonography and more recently cine MR to assess for tethering and decreased motion [52, 53]. Yamada et al. have proposed the assessment of anal sphincter tone and posterior displacement of a normally positioned conus as criteria for diagnosis [54]. However, there is an almost complete lack of normal or pathological reference data with which to determine the sensitivity and/or specificity of these tests. Until such validation emerges, surgical management of OTCS will continue to be based largely on provider preference and clinical judgment. Nevertheless, the surgical management of OTCS is now established practice in some centers, and the main challenge for the future will be to establish more concrete diagnostic criteria. These criteria will require large cohorts comprising separate surgically and conservatively managed study arms if they are to achieve the necessary impact. However, given the previously established benefit of untethering in the context of symptomatic cord stretching, the question becomes one of ethics. Appreciating the current landscape of surgery for OTCS, some centers manage virtually every patient surgically, while others manage none in this manner. One option would be to match OTCS surgical centers to nonsurgical centers through registries and to measure standardized outcomes between their respective patient populations. However, as we slowly approach the realization of large-scale surgical series for OTCS and the need to juxtapose "OTCS" presentations against the accepted "standard" TCS presentations, it would be sensible to begin by examining what most of the pediatric neurosurgery community considers to represent standard of care in the diagnosis of TCS, the evolution of its management, and how these standards were reached. It would be unwise either to adopt or to reject indications for a procedure (e.g., OTCS) without reasonable knowledge of the burden of evidence used to establish similar indications for a comparable standard of care (TCS).

The Standard of Care of TCS

First described nearly two centuries ago, TCS has had a uniquely controversial history. Pioneered during an era of widespread surgical discovery, it is possible that cord untethering to treat TCS has been grandfathered into current clinical practice and has yet to be viewed through the modern lens of evidence-based medicine. With a more procedurally permissive blurring of lines driven by OTCS, some might wonder at the percentage of TCS diagnoses that have resulted in unwarranted surgical intervention over the years. This concept of overtreatment is of growing concern in healthcare

with examples in many disciplines. For example, the overdiagnosis of invasive breast cancer among women in their 50s is estimated to be as high as 54% [55, 56]. Similarly, in the context of a steadily rising incidence of thyroid cancer since 1973, many new diagnoses have been of smaller and less aggressive cancers requiring no treatment [57]. Nearly every example is a result of improvements in screening and diagnostic technology, which inevitably result in increased detection of subclinical disease. This, in turn, leads to an overestimation of the benefits of certain therapies based on the treatment of milder disease forms. The evolution of TCS, in contrast, has not followed this pattern; diagnosis has been largely led by natural history data demonstrating deterioration over time in the absence of surgical intervention, which easily outweighs the fairly low risk of surgical complications in the context of relatively simple defects (e.g., tight filum terminale, dermal sinus tract) [58–64]. It is not the purpose of this chapter to review the surgical indications of TCS, as these studies are reviewed elsewhere in this book. However, a sense of generalization of both the therapeutic benefits of surgery and the detrimental effects of conservatism seems to have permeated the literature inextricably during the last three decades. On the one hand, this eventually led to the scientifically unproven concept of OTCS being encompassed within the surgical armamentarium; at the other extreme, it led equally conscientious surgeons to question the status quo and state that surgery is seldom, if ever, necessary in any of these disorders [65–67]. It may be time for large cohort studies and registries to help us determine not only what works or does not work but, more importantly, what is appropriate in the context of specific diagnoses (tight filum terminale, split cord malformation, lipomyelomeningoceles, and even lipomyelomeningocele subtypes, etc.), age, imaging findings, and symptomatic states. As has been demonstrated in other medical disciplines, the answer is likely to prove more complicated than assumed by either school [68–70].

Does This Represent a Larger Problem?

First announced in the early 1990s, evidence-based medicine is a relatively new paradigm aimed at improving healthcare. Evidence-based medicine is defined as "the conscientious and judicious use of current best evidence in conjunction with clinical expertise and patient values to guide health care decisions" [71, 72]. What constitutes "best evidence" is assessed on the basis of different levels of evidence, with systematic reviews topping the list. As is the case with TCS, "when definitive evidence is not available, one must fall back on weaker evidence" and ultimately accept "that physicians who are up-to-date as a function of their ability to read the current literature critically… are able to distinguish strong from weaker evidence… are likely to be more judicious… [and] make more accurate diagnoses" [72, 73]. Can we truly claim that this is the case for OTCS? The cliché "hindsight is 20/20" can be applied broadly in the history of medicine and especially surgery. Although we cannot look into the future to identify our current follies, we do possess foresight, the full potential of which we cannot achieve without an honest look at our practices and a reassessment of what we do and why.

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Dermal Sinus Tracts

9

Zachary G. Wright and Curtis J. Rozzelle

Introduction

Dermal sinus tracts (DSTs) are congenital malformations of the spine in which a tract of epithelial tissue extends from the skin through the subcutaneous tissues sometimes as deep as the thecal sac and deeper to the spinal cord. DSTs are clinically relevant for several reasons. They create a communication between the thecal sac and the outside world that predisposes patients to infection. Additionally, such tracts can tether the spinal cord and can cause the formation of associated masses, e.g., dermoids. Lastly, they may be easily overlooked, with only a small sinus ostium present on the skin, though they may also have stigmata such as skin dimples, pigmented changes, skin tags, focal hypertrichosis, or angiomata.

Epidemiology

DSTs are found in an estimated 1 in 1500–2500 live births [1, 2], with a distribution along the spine of 1% cervical, 10% thoracic, 41% lumbar, and 35% lumbosacral [3].

Embryology

Around day 15 of life, the embryo begins to form three tissue layers (gastrulation). The superficial ectoderm thickens, folds, and involutes rostrally to form Hensen's node (the primitive knot). Cells extend from the depths of Hensen's node and form

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paraxial mesoderm between the ectoderm and endoderm. Within the bundles of mesoderm, the notochord forms between the prechordal plate rostrally and the cloacal membrane caudally. The notochord induces growth of the neural plate and vertebral bodies.

The neural plate closes to form a neural tube between days 18 and 27 of life through primary neurulation. This begins at the rostral neuropore and continues caudally. The superficial cutaneous ectoderm and neuroectoderm are rigidly adherent until they separate during disjunction, allowing the neural tube to close and migrate ventrally, becoming surrounded with mesoderm dorsally.

A failure of disjunction during the fourth week of life can result in a rest of epithelial tissue remaining adherent to the neural tube. This forms a tract that begins on the surface of the skin and may terminate anywhere from the subcutaneous space to the intramedullary space.

As the growth of the vertebral column outpaces neural tube growth, the superficial dermal sinus ostium may end up several levels inferior to the deeper ostium.

The dermal sinus tract involves an inner layer of squamous epithelium from the superficial ectoderm and is encased by dermal and neuroglial tissue. Within these tracts a variety of cell types may be found, including nerve or ganglion cells, fat, blood vessels, cartilage, and meningeal remnants.

DSTs are often associated with other forms of spinal dysraphism such as myelomeningoceles, lipomyelomeningoceles, and split cord malformations. Dermoid and epidermoid tumors can appear within focal expansions in approximately half of all DST.

Pathophysiology

The sequelae of DSTs are variable and may overlap.

Tethering

The DST may act as a tether, causing defects in motor function, musculoskeletal development, and bowel and urinary bladder function.

Infection

DSTs provide a direct pathway from the skin to the thecal sac and can thus lead to an intradural abscess or meningitis. A history of recurrent otherwise unexplained meningitis should lead to a detailed search for a DST including a thorough physical examination of the skin overlying the spine from the sacrum to the occiput and MRI imaging of the neuroaxis.

Mass

DST can result in the formation of mass lesions by development of abscesses or as a result of disordered embryogenesis.

Associated Tumors of Disordered Embryogenesis

Formation of a dermoid or epidermoid tumor (also known as an inclusion cyst) along the DST is a result of continued cell division of the inner layer of the DST that is derived from the cutaneous ectoderm.

Epidermoid tumors contain only epidermal tissue, while dermoids may contain dermal elements such as hair follicles and/or elements of sweat glands.

Clinical Presentation

Superficial Abnormalities

The most common reason prompting neurosurgical referral and diagnosis of a DST is a skin lesion [4]. Skin findings include simple dimples, pigment changes, raised plaques, skin tags, subcutaneous lipomas, and angiomata (Figs. 9.1 and 9.2). Skin findings were found in 27 of 28 patients in one series [4]. Skin findings were the most common presentation in infants less than 1 year old.

DSTs usually terminate superficially as a midline cutaneous pit or dimple above the intergluteal crease. These should be differentiated from pits below the top of the intergluteal crease, which are simple benign sacrococcygeal pits, encountered in 5% of normal patients.

Foot abnormalities appeared in 4 of 28 patients.

Neurological Deficit

In one series, 8 of 28 patients were referred for neurologic deficits, but 19 were found to have such deficits on initial neurosurgical evaluation including weakness, sensory changes, reflex changes, gait changes, decreased sphincter tone, or difficulty with bowel or urinary bladder function [4]. Of infants less than 1 year old, 8 of 16 had neurologic deficits, while 11 of 12 greater than 1 year old had such deficits. Such deficits are typically due to neural compression from inclusion tumors or tethering of the spinal cord due to the DST. Rapid neurologic deterioration suggests infection within dermoid tumors [5].

More gradual deterioration due to a DST may present similarly to other forms of occult spinal dysraphism, including pain, scoliosis, gait abnormalities, orthopedic deformities, sensory deficits, asymmetric weakness, and patchy sensory loss [5].

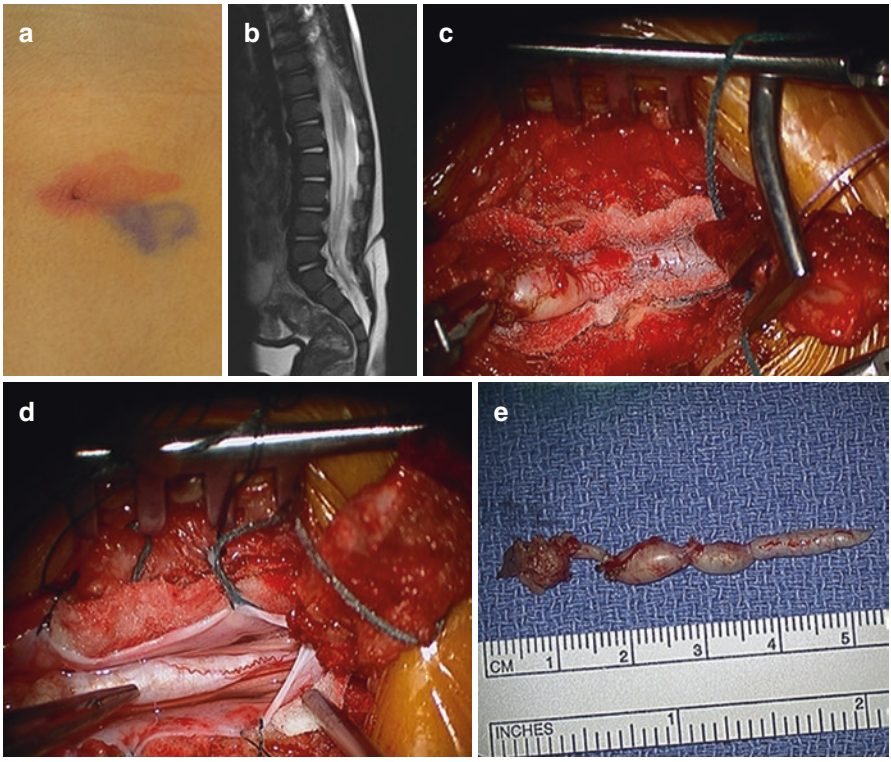

Fig. 9.1 A 9-month-old boy imaged due to lumbar cutaneous stigmata. (**a**) Skin dimple with hemangioma. (**b**) T2 sagittal MRI demonstrating subcutaneous course of DST. (**c**) Intraoperative photograph demonstrating extradural DST. (**d**) Intraoperative photograph demonstrating intradural dermoid, tapering rostrally toward conus. (**e**) Completely excised DST with string of dermal expansions

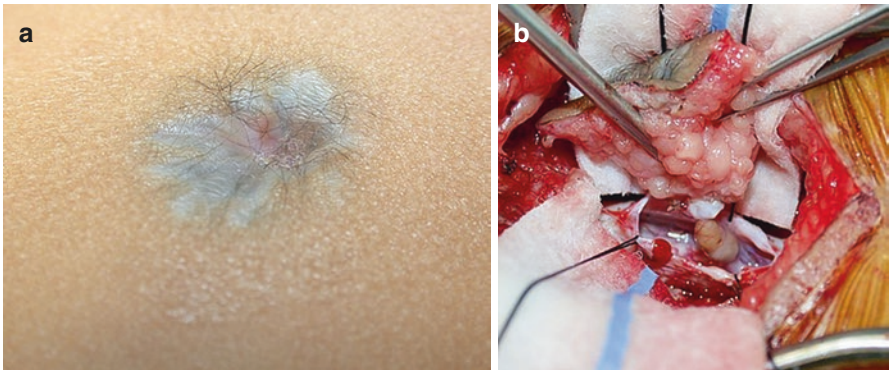

Fig. 9.2 (**a**) Small dorsal midline tuft of hair with skin dimple, mid-thoracic level; asymptomatic 2-year-old female. (**b**) DST dissection from the skin to dorsal spinal cord attachment (black sutures through cut edges of dura)

Infection

Infection is a classic presenting sign of DST, particularly prevalent in older accounts but also common in more current series [6, 7]. Infection can manifest as meningitis or as an abscess that may be epidural, subdural, or intramedullary (Fig. 9.3). Recurrent meningitis should prompt a clinician to consider DST.

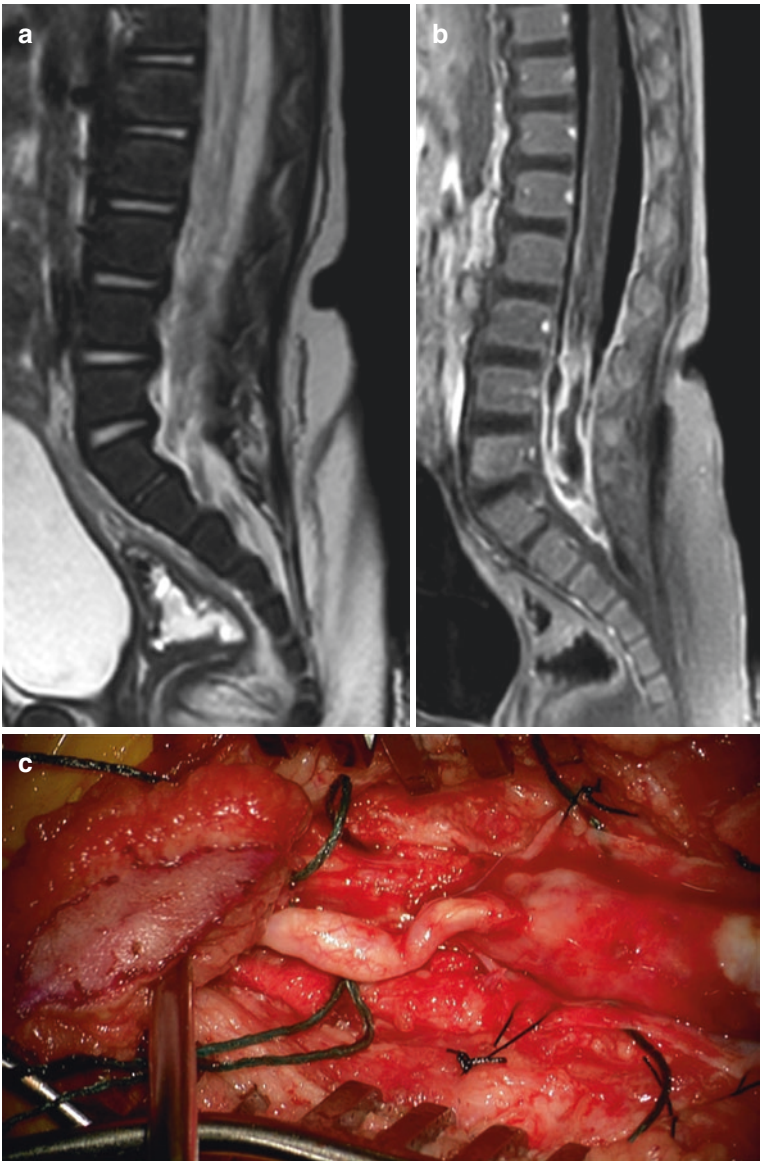

Fig. 9.3 A 5-year-old boy with persistent meningitis despite antibiotic therapy. (**a**) Sagittal T2 MRI demonstrating subdural tract and extensive hypointense signal in region of cauda equina. (**b**) Gadolinium-enhanced T1 sagittal MRI demonstrating intrathecal abscess. (**c**) Intraoperative photograph demonstrating infected DST from the skin to intrathecal abscess

Occasionally, the leakage of irritative dermoid or epidermoid elements may cause recurrent sterile meningitis [5].

Diagnostic Studies

MRI is the diagnostic study of choice for those patients with suspected DST, though abnormalities may also be noted on CT (computed tomography), radiographs, and ultrasound.

MRI is useful for delineating the anatomy of large associated dermoid or epidermoids but cannot be relied on to identify intradural extension of the DST or smaller inclusion tumors. In one series, intradural tracts were seen in 46% of MRI of DST patients, while a dermoid was preoperatively identified in 15%. Intraoperatively, intradural tracts were found in 86% of cases and intraspinal dermoids in 24% [8].

Dermal Sinus-Like Stalks

Various terms that may or may not be equivalent to DST include dermal sinus-like stalk, pseudo-dermal sinus tract, meningocele manqué, rudimentary meningocele, limited dorsal myeloschisis, hamartomatous stalk, and fibrovascular and meningothelial tract [9–12]. These entities do not have an epithelial cell-lined lumen. Instead they contain fibrovascular tissue of mesodermal origin such as fibrous tissue, adipose tissue, neural tissue, blood vessels, ependymal elements, cartilage, muscle, and meningothelial tissue [9]. They present with similar cutaneous stigmata to DST but tend to have a cutaneous opening covered with a thin translucent layer of the skin with a "cigarette burn" appearance [9, 11]. Like DST, the depth of the stalk is variable.

The neurological presentation is similar to that of DST; however they do not present with infectious sequelae as there is no lumen to provide a pathological communication. Dermoid or epidermoid tumors are more typically associated with DSTs but may be associated with dermal sinus-like tracts as well [12]. Dermal sinus-like stalks are also associated with thickened fila or lipomas.

There are no reliable radiological features that can be used to distinguish a dermal sinus-like stalk from a DST. In this context, as the cutaneous stigmata are variable, it is difficult to distinguish DST from dermal sinus-like stalks. It is, therefore, prudent to treat suspected dermal sinus-like stalks with prompt excision.

Treatment

Timing of Surgery

Resection of a DST is urgent. Meningitis and an intraspinal abscess are potentially devastating consequences of DST. In those patients who have already contracted

meningitis due to DST, antibiotic therapy is typically administered to allow for a less inflammatory environment in which to operate in the hopes of decreasing the risk of scarring and retethering. In those who have not contracted infection, there is a risk of infection with each further day without definitive treatment, and these should thus be treated as soon as possible. Patients presenting with a neurologic deficit due to an abscess associated with a DST are rare but represent a true neurosurgical emergency.

Surgical Technique

An incision is marked in the midline extending both above and below the ostium of the DST. At the level of the DST, the incision is elliptical, isolating the DST. Once this is made, care is taken during the dissection to isolate but not interrupt the DST (Figs. 9.1 and 9.2). This is carried forward until it reaches the deep fascia, where, again, an elliptical incision is made around the entrance of the DST, and this continued in the midline superior and inferior to the DST entrance. A subperiosteal dissection is performed with electrocautery from the first normal spinous process and lamina. The DST is followed through the deeper tissues and laminectomy performed with care taken to preserve the DST which may enter between laminae or through a spinous process.

The dural opening is performed elliptically as with the skin and fascial openings and the DST followed until it terminates. In lumbosacral DST, the tract may continue superiorly for several levels requiring extension of the skin, fascial, bony, and dural openings. Failure to dissect and follow the tract to its termination at the spinal cord may leave epithelial tissue that risks subsequent growth of a dermoid cyst.

If the DST is lost leading up to exposure of the thecal sac, the dura mater should still be opened and explored for the DST to ensure that there is no remnant with inspect for adhesions, dermoid tumors, or a thickened filum terminale.

Dermoid or epidermoid cysts should be resected wherever they are encountered during the surgical dissection. If they are encountered intradurally, the dissection must be performed with care, minimizing traction on the nerve roots and conus medullaris by using sharp dissection.

Neuromonitoring may be useful in distinguishing nerve roots within a mass of inclusion tumor. Modalities include motor- and somatosensory-evoked potentials and muscle and external anal sphincter electromyography.

Following resection of the DST and any associated inclusion tumors, the dura mater is typically closed primarily in a watertight fashion though patch grafting has been described with the goal of reducing the incidence of postoperative scarring with resultant tethering of the spinal cord [5].

Postoperative Care

Patients should be kept flat for 1–3 days to allow for adequate wound healing before being mobilized. Close inspection of the wound is important with particular

attention to swelling indicating pseudomeningocele formation as well as cerebrospinal leaks from the incision.

Outcomes

The outcome from DST resection is generally good. Patients without neurological deficits typically remain intact, and patients with preoperative neurological deficits typically improve or stabilize. There are risks of cerebrospinal fluid leak, neurologic deficit, or recurrence of dermoid or epidermoid tumors, but these can be limited with careful planning and technique.

In those patients in whom a residual dermoid element is left adherent to nerve roots or the conus medullaris, interval follow-up imaging is recommended.

Conclusions

DSTs are rare congenital disorders characterized by a failure of disjunction of the neuroectoderm and cutaneous ectoderm causing a persistent communication from the skin to the neuroaxis.

Cutaneous stigmata of DST include hypertrichosis, dimples, pigment changes, raised plaques, skin tags, and angiomata. Lumbar DSTs are characterized by upwardly directed tracts above the level of the gluteal fold, whereas sacral pits are downwardly directed and below the level of the gluteal fold.

Complete dissection of DSTs to the level of the spinal cord prevents the future development of dermoid tumors or epidermoid inclusion cysts along the length of the tracts.

Treatment of DST with complete surgical excision is the standard of care and is associated with excellent outcomes particularly if undertaken early in the life of the patient.

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Spinal Neurenteric Cysts

10

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History and Nomenclature

Neurenteric cysts (NECs) are rare benign cystic lesions of the central nervous system (CNS) that are derived from the endoderm. These lesions were first described by Puusepp in 1934 as "intestinomas" [1]. They have been given various alternative names in the literature such as enterogenous cysts, enteric cysts, endodermal cysts, bronchogenic cysts, gastroenterogenous cysts, gastrocytomas, and archenteric cysts [2–6]. Although the World Health Organization (WHO) prefers the term "enterogenous" in the revised classification of CNS tumors, the term "neurenteric cyst" is the most widely accepted in the neuropathology literature [5–7].

Epidemiology and Location

These cystic lesions occur among all age groups with no gender predilection.

A case of dorsal neurenteric cyst has been reported in a 2-year-old patient who also had an infection within the cyst, with evidence of paraspinal extension [8]. NECs can occur anywhere along the neuraxis, but spinal NECs are about three times more frequent than intracranial ones [2, 9]. They represent about 0.7–0.3% of all spinal tumors [10]. They are usually found ventral to the cord. Spinal NECs are most often found at the lower cervical or upper thoracic level [11], although a few authors have reported rare occurrences at the craniovertebral junction and the lumbar spine [12, 13]. Most intraspinal NECs are located in the intradural extramedullary (IDEM)

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compartment of the cervicothoracic junction and are often associated with bony, soft tissue, and visceral abnormalities. They occur in the intramedullary compartment in only <5% of cases [12–14]. About 50% of cases are associated with vertebral body anomalies such as hemivertebrae and kyphoscoliosis [10, 15, 16]. Associations with bony defects such as spina bifida, split cord malformation, and Klippel-Feil syndrome are not uncommon [10].

Intracranial NECs are rare (about 0.01–0.35% of all CNS lesions) and only about 100 cases have been reported in the literature to date [2, 17, 18]. The posterior fossa is the most common intracranial location, accounting for approximately 70–90% of intracranial NECs [18, 19]. They are typically found in the midline, often anterior to the brain stem (23.1–51%), the cerebellopontine angle (17–51%), or inside the ventricles [20]. Only a few cases of NECs have been reported in rare supratentorial locations such as the suprasellar [21, 22] or the parasellar [18, 23] regions, along the optic [24] or the oculomotor [25] nerve, in the superior orbital fissure, [26] or as intraparenchymal- or dural-based lesions [27, 28]. In contrast to their spinal counterparts, intracranial NECs are seldom associated with bony anomalies, only one case report showing erosion of the petrous temporal bone adjacent to the cyst [18, 20, 29].

Various Embryological Explanations for the Development of NECs

The exact etiology of NECs remains unknown [3, 30], but several hypotheses have been proposed [3, 9, 18, 31–33]. These cystic lesions are thought to arise from faulty development of the neurenteric canal. During early embryogenesis, there is transient communication between the primitive neuroectoderm and endoderm. Around the 3rd week of gestation, if the notochord and foregut fail to separate during the process of escalation, primitive endodermal cells are incorporated into the notochord [3, 4, 29]. These displaced nests of alimentary tissue ultimately generate the components of the cyst. Smith proposed a classification system depending upon the extent of persistence of the neurenteric canal. The spectrum of variability in the composition of an NEC ranges from the most innocuous congenital dorsal enteric sinus to a dorsal enteric fistula, where the entire neurenteric canal remains patent [34]. The clivus forms the cranial margin of the endoderm in an embryo; this can account for the origin of spinal NECs caudal to the clivus, but the origin of supratentorial NECs remains unexplained [29].

Some authors believe that supratentorial NECs arise from the endodermally derived Seesel pouch, a midline diverticulum located behind the oropharyngeal membrane. This hypothesis is supported by the fact that NECs have similar immunohistochemical staining properties to those of Rathke's cleft cyst and colloid cysts, positive for epithelial membrane antigen (EMA), carcinoembryonic antigen

(CEA), and cytokeratin and negative for glial fibrillary acidic protein (GFAP). However, this still fails to explain the development of off-midline cysts [17, 18, 21, 35, 36].

Clinical Presentation

Spinal NECs occur among a wide range of age groups from the neonatal period to the eighth decade. There is a bimodal age distribution with a small peak found in the first decade and a larger second peak in the third to fourth decade with no gender predilection [37].

The most common overall location of NECs is the posterior mediastinum [22, 37, 38]. They can connect the CNS to the mediastinum or abdominal viscera [22, 38]. The spinal canal is the second most common site. Spinal NECs are usually located ventral to the cord; dorsally placed ones are very rare [8]. About 50% of them are associated with such anomalies as dysraphism, hemivertebrae, and VACTERL anomalies (vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities). NECs constitute less than 1% of all spinal tumors [11, 37]. Sometimes they occur near the lower clivus, in the medulla oblongata, at the parietal convexity, and within the optic nerve; they can even be extradural [24, 37, 39–42].

NECs can present as incidental space-occupying lesions on magnetic resonance imaging (MRI) (Figs. 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, and 10.7). When symptomatic, the onset of symptoms can range from a week to 10 years prior to diagnosis [38]. They commonly present with nonspecific symptoms predominantly depending upon the anatomical location of the lesion, such as focal neurological deficits, seizures, cranial nerve palsies, gait disturbance, ataxia, myelopathy, radicular pain, and incontinence. They can manifest as memory disturbances, obstructive hydrocephalus with features of raised intracranial pressure (ICP) [43], and rarely with atypical presentations such as an acute onset of symptoms, recurrent episodes of myelo-radiculopathy, or aseptic meningitis resulting from microleakage of cyst contents [13]. The most common presenting symptom is headache. These symptoms can result from chronic inflammation or irritation of the surrounding structures or to the local mass effect [22, 44]. They are usually benign lesions with a slow growth potential; however, rapid expansion can result from hemorrhage, inflammation, or increased secretion of fluid content within the cyst [37]. Sharma et al. observed acute-onset, rapidly progressive quadriparesis with respiratory failure in a ventrally placed foramen magnum NEC, which required emergency life-saving surgical decompression [12]. Malignant transformation of a NEC is very rare, with only six cases reported in the literature [45–47]. NECs with rare presentations and with nonspecific symptoms pose a diagnostic challenge.

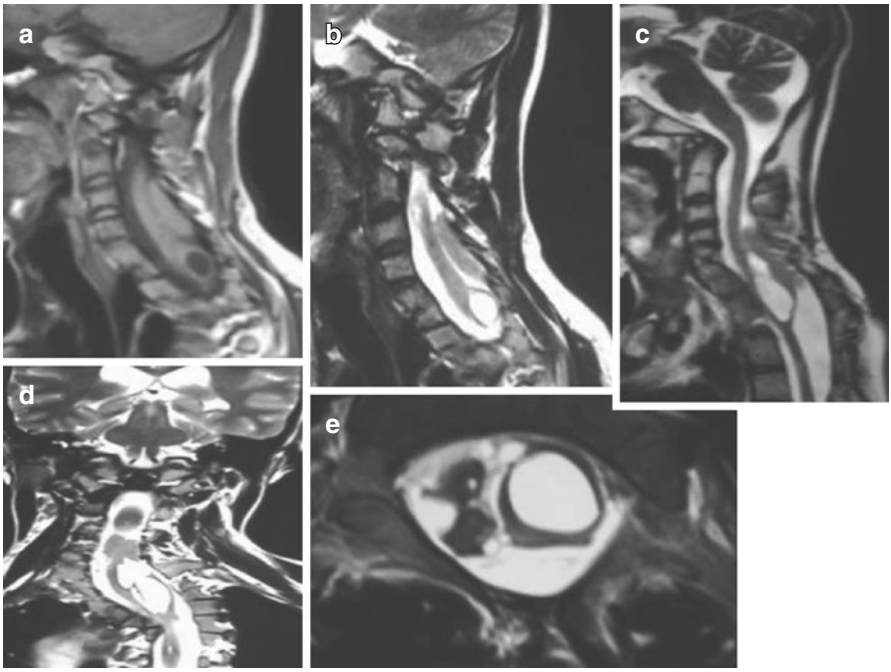

Fig. 10.1 Typical radiological findings in a spinal neurenteric cyst. A well-defined intramedullary cystic lesion can be seen extending from C6 to D3. The cystic lesion is (**a**) hypointense on T1-weighted image; (**b**) hyperintense on T2-weighted image. (**c**, **d**) It causes fusiform enlargement of the spinal cord. The C5 and C6 hemivertebrae exhibit scoliosis toward the right side. (**e**) A large intramedullary cyst is visible in the axial section

Histopathological Classification

NECs usually appear as thin-walled transparent cysts containing a gelatinous fluid, yellow or milky-white in color on gross inspection. They have been described as having a variable appearance under light microscopy. There are two predominant histological variants: [3, 5] (1) pseudostratified, ciliated, columnar-to-cuboidal epithelium with scant mucin-producing cells (17%); and, (2) simple, nonciliated epithelium with abundant mucin-producing cells (50%). The only consistent radiological finding with a pathological correlate is T2 hypointensity associated with elevated protein concentration in the cyst fluid [29]. The cyst fluid is often clear, yellowish, or brown; it is oily and contains histiocytes, cholesterol crystals, and keratin debris. Various other pathological features such as foamy histiocytes with chronic inflammatory cells [48], amyloid deposits in the cyst wall [37], and a xanthogranulomatous change [49] have been reported. Occasionally, there is squamous metaplasia.

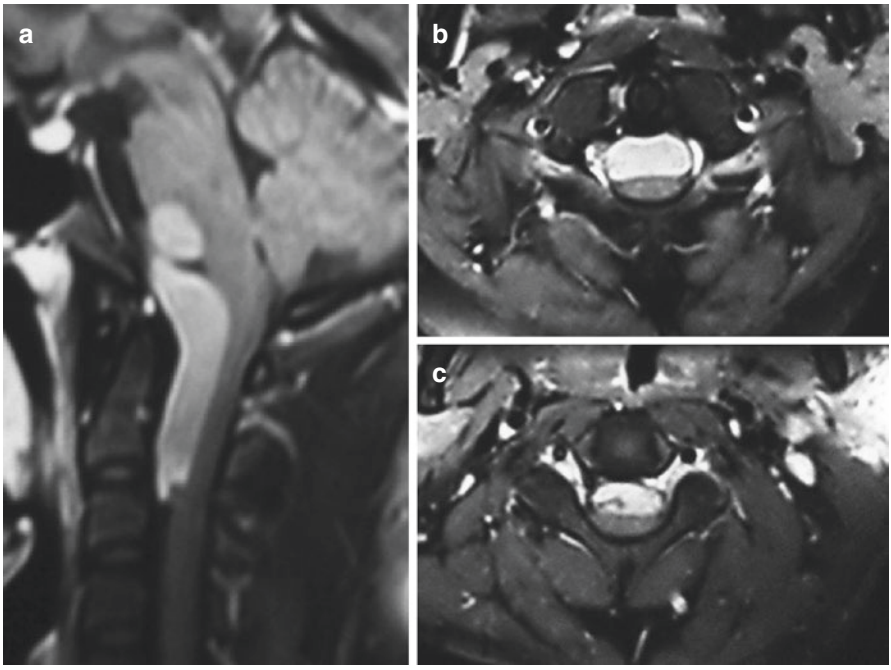

Fig. 10.2 (**a**) Contrast T1 sagittal MR image of the craniovertebral junction (CVJ) showing an anteriorly placed neurenteric cyst with an indentation caused by the traversing vertebral artery. (**b**, **c**) Contrast-enhanced axial T1 MR images showing the lesion situated anterior to the cervical cord. (From Shukla et al. [14]; with permission)

Three histological types of spinal NEC can be distinguished according to the Wilkins and Odom classification (Table 10.1) [50]. Type 1 cysts resemble respiratory or gastrointestinal epithelium and are covered with a single or pseudostratified layer of ciliated or nonciliated cuboidal or columnar epithelium with a basement membrane overlying the fibro-connective tissue. Type 2 cysts are richer in connective tissue and can include smooth muscles, glandular and lymphoid tissues, and rarely nerve ganglia, in addition with all the features of type 1 cysts. Type 3 cysts are similar to type 2 with the addition of ependymal or glial elements. Anteriorly placed intracranial cysts are usually type 1, while posteriorly placed ones are often type 2 or type 3 and are more likely to be associated with congenital anomalies (Fig. 10.8) [16].

NECs are typically benign; however, de novo malignancy, and even malignant transformation to mucinous low-grade adenocarcinoma [51], invasive mucinous papillary cystadenocarcinoma [45], or a well-differentiated papillary adenocarcinoma [52], can occur. A supratentorial NEC can coexist with an intraparenchymal subependymoma [53].

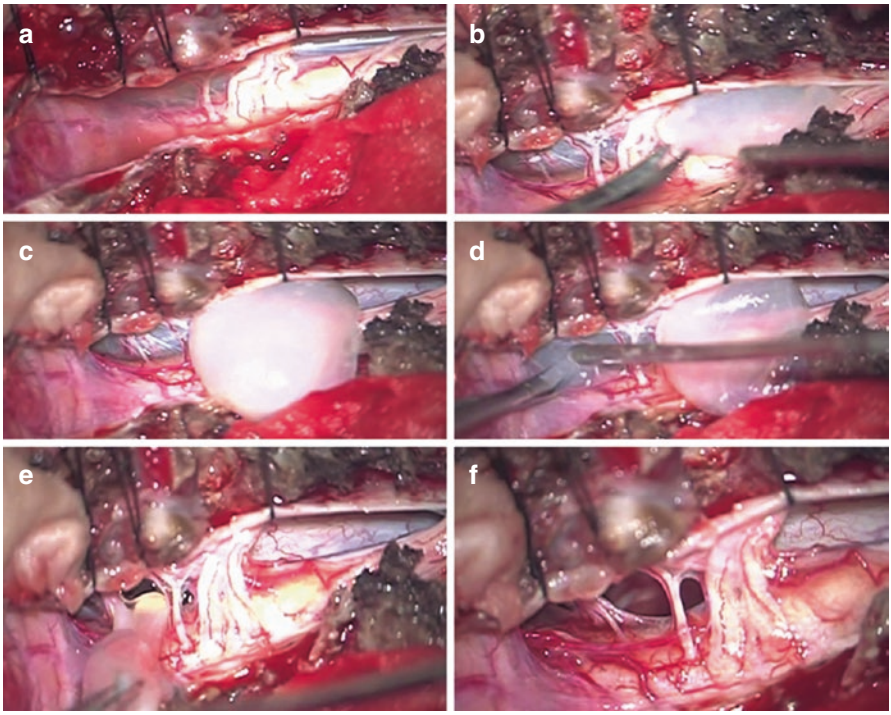

Fig. 10.3 Intraoperative images showing the lesion undergoing a right-sided far lateral approach without vertebral artery mobilization. (**a**) The medulla and upper cervical cord are compressed by an anteriorly placed cyst covered with arachnoid membrane. The cyst lies both superior and inferior to the origin of the lower cranial nerves. (**b**, **c**) The arachnoid anterior to the upper cervical cord is opened to reveal the inferior part of the neurenteric cyst. (**d**) Opening the arachnoid above the lower cranial nerves reveals the upper part of the neurenteric cyst. (**e**) The lower part of the cyst is excised. The capsule of the upper part is delivered, and the fibrotic band adherent to the anterior cord is visible; (**f**) the entire cyst has been excised, and the vertebral artery can be seen in the depth anterior to the cervicomedullary junction. (From Shukla et al. [14]; with permission)

Use of Immunohistochemistry (IHC) in Diagnosis

Immunohistochemistry is important in establishing the diagnosis, particularly if the radiological findings are nonspecific. The epithelia of NECs stain positive for anti-EMA antibodies, anti-cytokeratin monoclonal antibodies, and anti-carcinoembryonic antigen antibodies [8], suggesting an endodermal origin. They stain negative for neuroectodermal markers such as GFAP, S100, neuron-specific enolase, and vimentin [22]. There is no NEC-specific marker. Periodic acid Schiff (PAS), mucicarmine, and Alcian blue stains can also be used to demonstrate secretory granules in the goblet cells, again signifying an endodermal origin. Some authors have reported carbohydrate antigen (CA) 19-9 positivity in benign cysts as well as in those that have undergone a malignant transformation. The titers of CA19-9 in the cerebrospinal fluid (CSF) increase in recurrent cysts, so this could prove to be an important biochemical surveillance marker [54, 55].

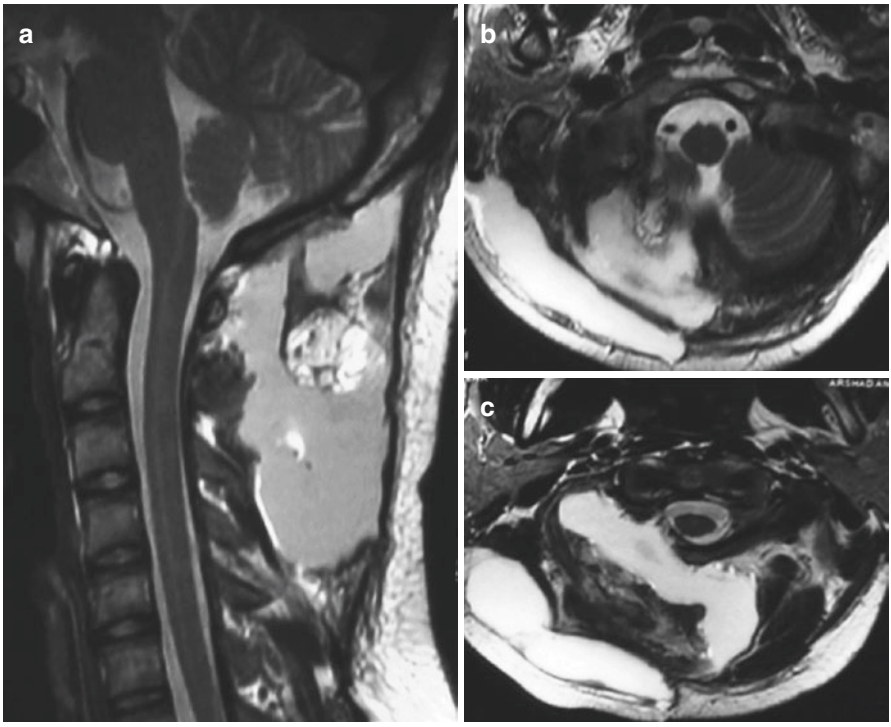

Fig. 10.4 (**a**) Postoperative T2 sagittal and (**b**, **c**) axial MR images showing total cyst excision by the far lateral approach. (From Shukla et al. [14]; with permission)

Diagnostic Imaging

Detailed radiological examination of the vertebral anatomy is essential in the treatment plan. The classic NEC, according to the literature, is usually less than 2 cm in size, a well-demarcated, lobulated cystic lesion with smooth borders and without contrast enhancement, found in extra-axial, intraparenchymal [35], or intraventricular locations [35, 56–58]. NECs most commonly appear as hypodense non-enhancing lesions on computed tomographic (CT) imaging. However, they can appear hyperdense or sometimes isodense to the surrounding brain parenchyma, posing a diagnostic dilemma. Some authors have reported that these cysts show peripheral wall enhancement [18, 29].

MRI is the radiological imaging method of choice. The signal intensity on MRI varies with the protein content of the cyst. It is typically T1 isointense to slightly hyperintense and hyperintense on T2-weighted imaging (WI) (Fig. 10.1). A case series has reported T1 hyperintensity (hyperintense to CSF) and T2 hyperintensity in 88.9% of cases. T2 hypointensity is described in the other 11.1%. High protein and xanthogranulomatous change can result in very high signal intensity on T1WI. T2 hypointensity in NECs has been reported in a few cases with squamous metaplasia (Figs. 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, and 10.7) [29]. The cysts appear as

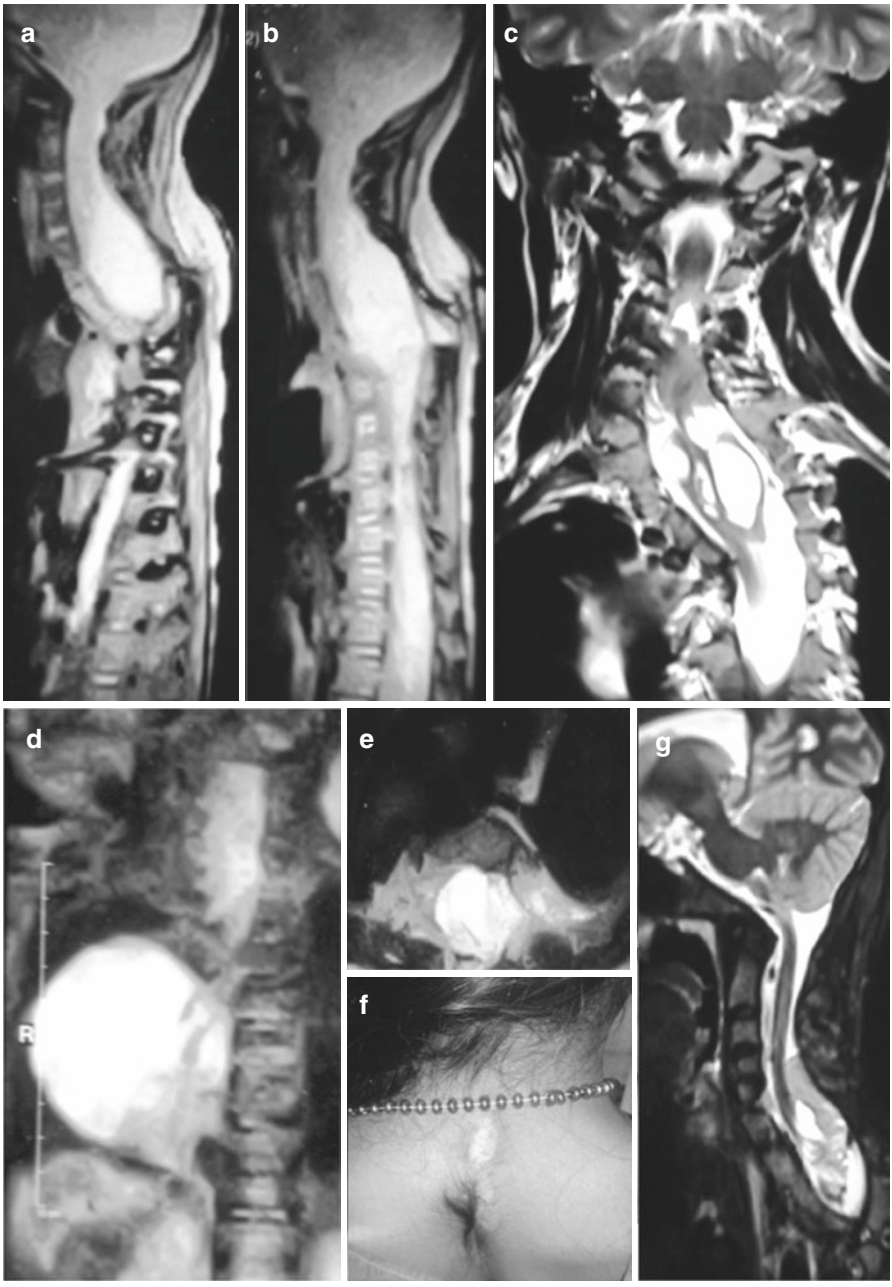

Fig. 10.5 An intradural extramedullary neurenteric cyst at the cervicothoracic region. (**a**, **b**) T2 sagittal and (**c**) T2 coronal image showing the cyst with cervicothoracic scoliosis with split cord malformation and abnormal dilatation of the spinal canal at the same level. (**d**) T2 coronal MR image of the thoracic spine showing a right-sided posterior mediastinal cyst. (**e**) T2 axial MR image showing asymmetrical dilatation of the cervical canal and an anteriorly placed neurenteric cyst. (**f**) Hypertrichosis with spina bifida. (**g**) T2 sagittal postoperative image shows excision of the cyst. There is persistent syringomyelia. (From Shukla et al. [14]; with permission)

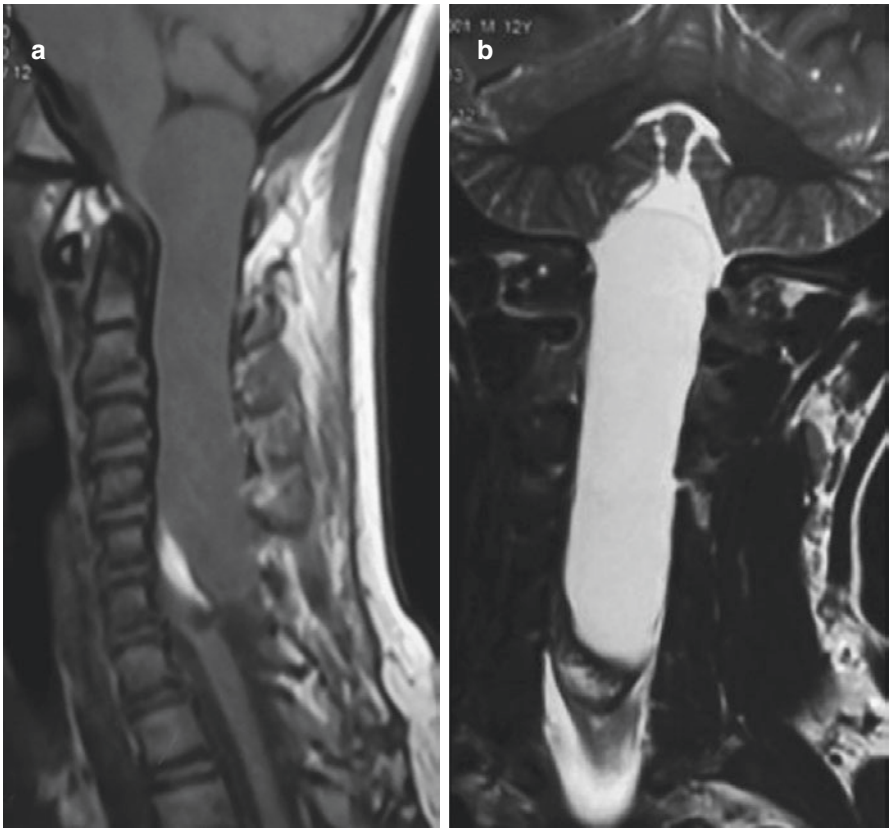

Fig. 10.6 (**a**) T1 sagittal and (**b**) T2 coronal MR images showing a long segment neurenteric cyst extending from the cervicomedullary junction to the cervicothoracic junction posterior to the cord with an abnormally shaped vertebral body and an anteroinferiorly placed fibrolipoma, causing adhesion to the spinal cord. (From Shukla et al. [14]; with permission)

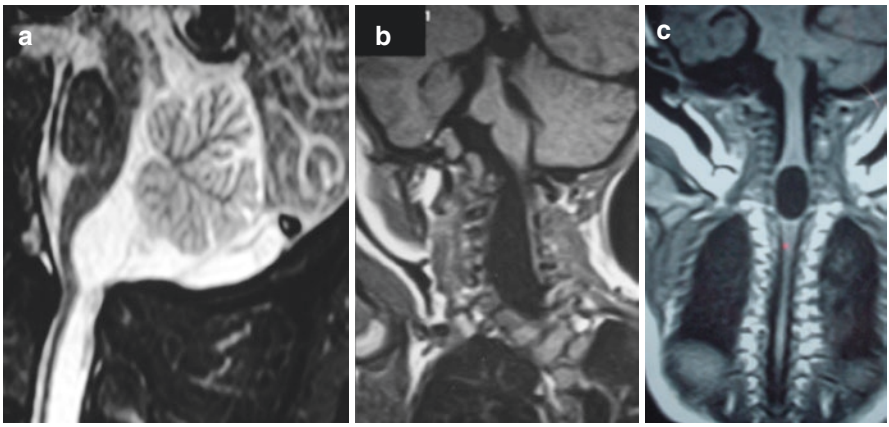

Fig. 10.7 (**a**) T2 sagittal MR image of a posteriorly situated cyst compressing the medulla and cervical cord. (**b**) T1 coronal image showing a patient with cervical scoliosis and a cervicothoracic hemivertebra with an anterolateral cyst causing cervical cord thinning. (**c**) An intramedullary neurenteric cyst. (From Shukla et al. [14]; with permission)

Table 10.1 Wilkins and Odom histopathological classification of spinal neurenteric cysts

Type	Characteristic features
Type A	Single layered pseudostratified ciliated columnar epithelium with basement membrane similar to respiratory or gastrointestinal epithelium
Type B	In addition to features of Type A – complex invaginations and organized glands producing mucinous or serous fluid, nerve ganglion, mesenchymal elements like muscle tissue, fat, cartilage, or bone
Type C	In addition to features of Type B – glial or ependymal tissue is also found

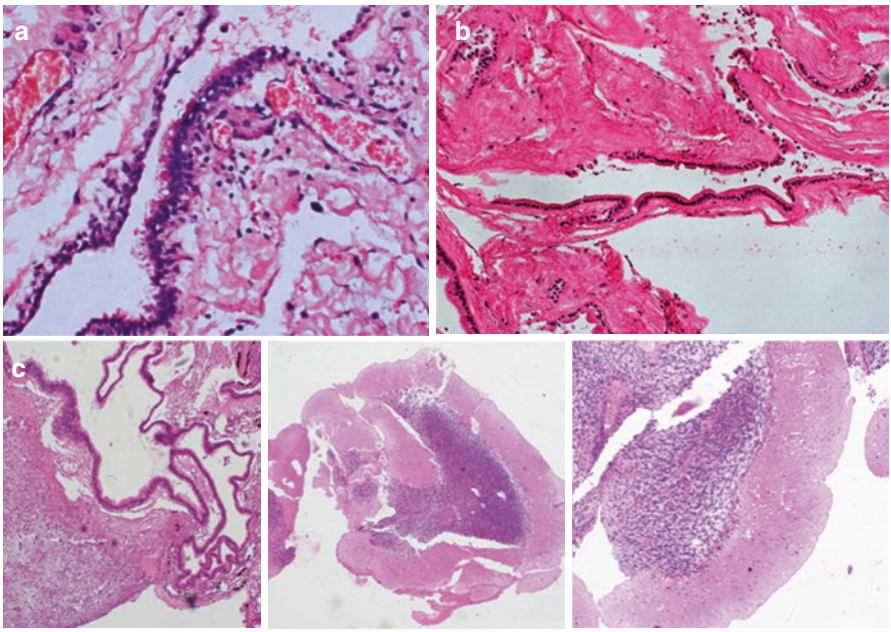

Fig. 10.8 Micrograph of a neurenteric cyst. (**a**) A cystic structure with the wall comprising fibrocollagenous tissue and lined with pseudostratified ciliated columnar epithelium and mucinous cells. The subepithelium shows congested vessels and mild mononuclear inflammatory cell infiltrate (hematoxylin and eosin X 400). (**b**) A type A cyst with pseudostratified ciliated columnar lining (hematoxylin and eosin X 100). (**c**) A neurenteric cyst containing cerebellar tissue (hematoxylin and eosin X 100). (From Shukla et al. [14]; with permission)

hyperintense lesions on fluid-attenuated inversion recovery (FLAIR) sequences with no perilesional edema. They can show mild restriction on diffusion-weighted imaging (DWI); however, frank restriction of diffusion has never been reported [59].

There is a characteristic large peak similar to N-acetylaspartate (NAA) on magnetic resonance spectroscopy (MRS) at 2.03 ppm despite the presence of neuronal contents in the cyst. The classical MRS peak is due to secreted contents and helps to differentiate the NEC from other cystic lesions [60]. A mural nodule is typically not seen in NECs; however, a "false" mural nodule can form as a result of epithelial cell secretion and epithelial cell desquamation [61, 62]. Other radiological features

such as rim enhancement [2, 29, 63–65], calcification [29, 31], and rapid expansion [37] of the cyst have also been reported. Supratentorial cysts are larger than their posterior fossa counterparts [29]. Hydrocephalus and other features of mass effect can also occur depending upon the location of the cyst. NECs can also be diagnosed in the prenatal period using MR imaging [66].

Differential Diagnosis

Owing to recent advances in neuroimaging, the reported incidence of NEC is rising. NECs need to be differentiated radiologically from other cystic lesions such as the epidermoid cyst, dermoid cyst, parasitic cyst (e.g., the hydatid cyst or neurocysticercosis), tumoral cyst, lipoma, neuroepithelial cyst, arachnoid cyst, other endodermal cysts (Rathke's and colloid cysts), cystic schwannoma, and craniopharyngioma [2, 16, 29, 67–69].

Epidermoid and dermoid cysts usually have irregular shapes, often encasing the adjacent neurovascular structures and infiltrating into contiguous cisterns. In comparison, NECs expand and displace the surrounding nerves and vessels. Dermoids can also be differentiated on the basis of fat suppression MRI imaging. Spinal epidermoid and dermoid cysts are usually located at the lumbosacral and cauda equina level and can have a (posterior) dermal sinus tract. Arachnoid cysts follow CSF intensity on all sequences. Other endodermal-derived cysts such as Rathke's and colloid cysts can be differentiated from NECs on the basis of their characteristic locations in the suprasellar region and the foramen of Monro region, respectively [70].

Craniopharyngiomas are hyperintense in T2-weighted images with bright contrast enhancement. NECs can be differentiated from neuroepithelial cysts by histopathological findings such as the presence of a basement membrane, cilia, and goblet cells with secretory granules. Neoplastic intramedullary lesions can be differentiated from these cysts by lack of contrast enhancement of the cyst wall and the absence of a mural nodule.

Surgical Management: Different Surgical Approaches

The goal of surgery for NECs is to alleviate the mass effect without causing dissemination, so complete excision of cyst is recommended. However, total excision is not always possible as the cyst wall is usually adherent to important structures such as the brainstem, spinal cord, cranial nerves and spinal nerve roots, and blood vessels. Small parts of the tumor capsule can persist and cause a recurrence with increased patient morbidity [14, 47, 71, 72]. There is a considerable recurrence rate from residual tumors, with the possibility of cranio-spinal dissemination and malignant transformation [14, 72].

The location of the cyst determines the operability, operative approach, and prognosis for the patient. For spinal NECs, there are three basic types of approaches – posterior, anterior, and lateral (Table 10.2). Each has its own merits and limitations.

Table 10.2 Different surgical approaches used for surgical excision of spinal neurenteric cysts in some of the major articles in literature

Serial no.	Studies	Location of spinal neurenteric cysts	Surgical treatment and approach
1	Song et al. (n = 1) [81]	Cervical spine	Lateral cervical approach
2	Abhishek et al. (n = 1) [82]	Intradural extramedullary ventrally located cystic lesion in cervical spine	Extreme lateral approach
3	Sasani et al. (n = 2) [83]	Cervical spine	Anterior approach
4	Laidlaw et al. (n = 1) [84]	Lower cervical spine	Ventral resection and anterior fusion utilizing sternal notch exposure
5	Tuzun et al. (n = 1) [85]	Upper cervical spine	Posterior approach
6	Liu et al. (n = 2) [86]	Cervicomedullary junction	Far lateral transcondylar approach
7.	Shukla et al. (n = 16) [14]	Cervicomedullary, cervical, thoracic, intradural extramedullary and intramedullary	Far lateral and posterior approaches

There is no consensus regarding the best approach, but the posterior approach is used most commonly worldwide. Even though most NECs are ventrally placed, the posterior approach provides an adequate surgical corridor. Various surgical options have been exercised such as cyst aspiration, cyst fenestration, partial excision, marsupialization, and cyst-subarachnoid shunting [73]. Owing to the high recurrence rate (0–37%), simple aspiration is not preferred.

Maneuvers such as cyst aspiration and cord manipulation can help in the surgery. Complications associated with this approach include cord or nerve root injury, epidural venous hemorrhage resulting in hematoma formation, and chances of cyst rupture leading to meningitis. The anterior approach using a corpectomy gives an anatomical advantage in the ease of accessing ventrally placed cysts, but additional instrumentation is usually required to provide stabilization. The anterolateral approach, which includes the far lateral and extreme lateral transcondylar approach at the foramen magnum (Fig. 10.3), the transpedicular and transfacetal approach with vertebral artery mobilization in the cervical spine, the costotransversectomy, extradural transpedicular approach, or the anterolateral approach at the thoracic spine is also reported in the literature. To access anteriorly placed lesions, the maneuvers adopted include turning the operating table obliquely to the contralateral side, a partial facetectomy along with lateral laminectomy, opening the dura in a T-shaped manner to connect the extradural and intradural portions anterolateral to the cord, sectioning of denticulate ligament at several levels, a good arachnoidal dissection, adequate cyst decompression from between the corridors provided by the nerve roots emerging from the spinal cord, and ensuring that the fibrous attachment of the tumor pedicle linking the last part of the tumor capsule to the spinal cord is divided carefully under vision. The cyst-cord boundary can easily be seen using this technique without cord manipulation or corpectomy.

Complete excision of a spinal NEC results in improvement of neurological symptoms in most (71%) cases [10]. Unfortunately, complete excision is not always achievable for intramedullary cysts, where the cyst wall is adherent to the spinal cord and there is no clear plane of dissection [74–76]. The extent of surgical resection must be weighed against the morbidity associated with the procedure. De Oliveira et al. have reported worsening of symptoms in 11% of their cases and failure to regain premorbid neurological function in 18% [38].

Surgical Outcome and Recurrence

Total resection of a spinal NEC often yields better improvement in associated motor and sensory deficits. After reviewing the case series of surgical outcomes of spine NECs, we found a worsening of symptoms in 11% of patients after surgical excision and failure to regain premorbid neurological function in 18% [76]. Although the literature on long-term outcomes is sparse, leading to a poor estimation of the true recurrence rate, the postsurgical recurrence mentioned ranges between 0% and 37%. Kim et al. and Cai et al. observed no recurrences in their case series of eight and seven patients, respectively [6, 77]. Holmes et al. observed recurrence in only 4% of their patients [38]. Chavda et al. reported the longest follow-up of 30 years and observed a 37% recurrence rate among their eight patients. Notably, all cases of recurrence in this study were in patients who had undergone partial surgical resection [74]. To date, the actual recurrence rate after partial resection of spinal NECs is unknown. Kimura et al. reviewed 18 cases with recurrent cysts. In 16 of them, only a partial cyst resection was achieved [71]. Paleologos et al. reported a case series in which there was no recurrence in patients who underwent gross total excision; in contrast, 11% of patients who underwent partial excision had a recurrence [78]. A similar trend was reported by Garg et al. No recurrence was observed in patients with gross total resection, whereas recurrence was seen in five out of eight (63%) patients with partial resection [13]. Menezes et al. found no correlation between recurrence and factors such as age, sex, cyst size, and level [79]. The estimated time gap for recurrent cysts to appear ranges from 2 months to 14 years after the initial partial resection. Therefore, a long-term clinical and neuroradiological follow-up is highly recommended [80]. There is no effective role for conventional radiotherapy and chemotherapy at present [80].

Consequently, the surgeon must try to achieve the primary treatment goal of gross total excision of the cyst contents and cyst wall while appreciating the possible morbidity associated with such a resection.

Conclusions

Spinal NECs occupy a particular part of the clinical spectrum of spinal diseases. These lesions display a characteristic histopathology, which includes a lining of well-differentiated columnar or cuboidal epithelium with or without cilia and mucus

globules. Patients with these heterotypic lesions of endodermal origin often present with myelopathy and/or radiculopathy. MRI is the gold standard for characterizing NECs and excluding other close differential diagnoses. CT scans are important for defining bony abnormalities that often coexist with displaced remnants of the developing gastrointestinal/respiratory tract. Complete surgical resection is the goal of treatment. However, the surgical plan must consider the merits and demerits of complete and partial resection in cases with no well-defined plane of cleavage between the cord and the cyst. With the documented recurrence rate as high as 37%, patients with partial resection of spinal NEC require regular clinical and radiological follow-up to test for re-accumulation of cyst contents.

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Lipomyelomeningoceles

11

Jeffrey P. Blount and Esther Dupepe

Introduction

Lipomyelomeningoceles (LMCs) are fat and fibrous masses that invade and tether the caudal spinal cord. They are the most common form of occult dysraphism and are among the most interesting and challenging lesions to face practitioners interested in developmental or spinal neurosurgery [1]. This is because there is incomplete understanding of the natural history of the untreated condition, and the pathological anatomy at the interface between the fatty-fibrous mass and the distal spinal cord is highly variable [2, 3]. The terminology used to describe LMCs is often inconsistent. The term "myelomeningocele" denotes an open, exposed placode that is absent, and the suffix "oma" in the most common alternative term "lipoma" implies neoplastic growth. These are not tumors which grow relentlessly and threaten by spread, local invasion, compression, or disruption of function. Rather, they are developmental lesions that arise from disordered neurulation [3–6]. Disordered neurulation gives rise to mesodermal mesenchymal tissues that intrude into an open neural plate and connect with and tether the middle of the conus medullaris or caudal spinal cord [7–9]. Surgical intervention can cause serious morbidity because the tissue planes between a fatty-fibrous lipoma and compromised neural tissue are often challenging to discern [10, 11]. Yet the natural history of untreated LMCs is widely considered to be ominous and associated with high levels of pain and progressive neurological decline [12–16]. Some authors suggest that partial resection of LMCs is worse for patient outcome than no surgical intervention at all

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[17]. Others advocate maximum "safe" resection for all but the most severely deteriorating patients [12, 15, 18–20], while still others advocate a conservative course until clear clinical deterioration is observed [21–23]. Papers from accomplished groups and centers advocate diametrically opposing points of view, embracing radical, complete resection with placode reconstruction versus nonoperative, conservative management as the preferred course. This "perfect storm" of differing opinions has given rise to confusion, uncertainty, and controversy among members of the neurosurgical community with regard to the surgical and monitoring techniques needed to optimize the affected patient's overall outcome.

Biology

LMCs arise from disordered neurulation (see Chap. 2) leading to fatty-fibrous masses that occupy variable amounts of space within the spine and lumbar soft tissue [4, 5]. Several classification schemes have been proposed, but each fails to characterize the extreme variability of LMCs simply yet adequately [7, 17, 24, 25]. The fatty tissue is mature adipose tissue arranged in a loose connective stroma histologically indistinguishable from normal adipose tissue [26]. Detailed analysis of large series has demonstrated rare mesenchymal elements such as muscle, nerve, and keratin and occasionally other ectoderm-derived tissues [26, 27]. This has led some investigators to consider all LMCs as variant forms of benign teratomas, but this concept has not been widely accepted and has limited practical utility [28]. These findings are more likely to attest to the early stage in development at which the critical pathophysiological events occur.

LMCs injure neural tissues in two ways [4, 29]. The first is by direct invasion of fatty tissue into the conus medullaris with direct disruption or replacement of neurons [1, 3, 9, 30, 31]. This is incompletely understood but is currently thought to result from premature detachment of the neural tube from the cutaneous ectoderm during primary neurulation. Fatty-fibrous tissue then replaces normal neural tissue in a cleft anomaly of the caudal and dorsal cord that variably extends rostrally to connect with the central canal of the spinal cord. Fatty-fibrous tissue displaces the overlying meninges, extends into the region of focal spina bifida, and fills the mesenchymal subcutaneous spaces of the back [9, 24, 30, 31]. Spinal lipomas occur when the fatty-fibrous tissue is confined to the subdural space and the meninges are largely or entirely preserved [26]. However, many writers and surgeons do not consider these distinctions and often use the terms lipomyelomeningocele (LMC) and spinal lipoma interchangeably. The extent of clinical deficit resulting from fundamentally disordered anatomical development is controversial, but it appears to be a significant and underreported (in surgical series) component of the overall burden of disease in LMCs.

The second way in which LMCs adversely affect normal neurological function is via tethering the spinal cord (TSC) [30, 32–34]. The traditional concept of TSC is that the fatty-fibrous mass connects the caudal end of the spinal cord to the surrounding soft tissue, thereby fixing the cord and preventing its normal ascent in response to disproportionate physiological growth between musculoskeletal and

neural spinal elements [34]. Fixation can also restrict the free movement that could dissipate the transmitted forces associated with normal activities of moving and stretching in daily living and perhaps even the force of pulsatile delivery of cardiac output to the nervous system [33]. The classic studies of Yamada showed oxidation was impaired in neural tissue subjected to longitudinal stress, though those studies have never been repeated or independently verified [34]. Clinically, progressive longitudinal stress and microtrauma give rise to pain and progressive impairment of the delicate reflexive arcs of the bladder and bowel and lower extremity motor function, which manifests as progressive incontinence and sensorimotor dysfunction of the lower extremities [34]. This is clinically referred to as tethered cord syndrome (TCS) [5, 33, 35].

Presentation

The presentation of LMCs is characteristically age-dependent. Infants and children harbor visible cutaneous anomalies over the midline lumbar spine [1, 3, 18, 19]. The most common manifestation is a visible asymptomatic or minimally symptomatic LMC, which presents as a painless, mobile subcutaneous lipoma of variable size in the midline lumbar region (Fig. 11.1). Various other skin abnormalities including capillary hemangiomas, dimples, and appendages are seen in most (>90%) cases (Fig. 11.2) [36–39]. Currently, virtually all patients with these findings are referred and evaluated in North America [1, 3]. Neurological function is variable, incompletely studied, and a source of controversy [23, 39, 40]. Most treated patients in surgical series with LMCs are described as neurologically normal at birth and in early life but decline over time [19, 32, 41]. Some series have found neurological and urological dysfunction in young patients. In many surgical series, patients who demonstrate symptoms at the time of surgery are considered to have symptom progression rather than symptom emergence. However, detailed clinical examination of

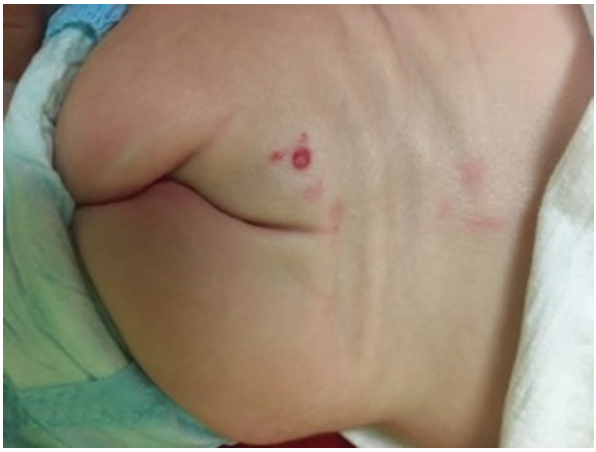

Fig. 11.1 Cutaneous hemangioma and deviation of gluteal crease with underlying small lipoma

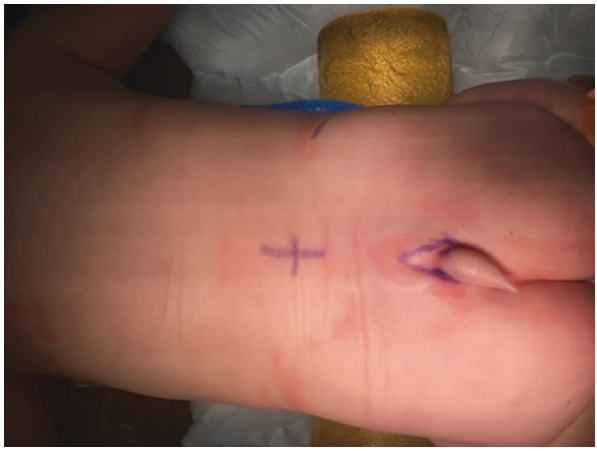

Fig. 11.2 Dermal appendage at proximal gluteal crease overlies focal lipoma with tethering

lower extremity and urological function in infants and young children is challenging, and some authors have suggested that symptoms can emerge rather than truly progress [22].

Teens and adults classically present with progressive neurological signs and symptoms. Most clinical series demonstrate more neurological impairment in older than younger patients. This is central to the fundamental premise that progressive neurological decline results from tethering and that surgical correction is effective in arresting such tether-related decline and conferring protection against it. Progressive dysfunction arises from tethering, and prevention of it provides the rational basis for all surgical efforts toward LMCs.

Imaging

Ultrasound

Ultrasound is of limited value for assessing LMCs and is characteristically reserved for dermal sinus tract evaluation and screening in the newborn infant. An ultrasound obtained on a patient harboring a LMC shows a region of homogeneous hyper-echogenicity.

MRI

The predominance of fat within LMCs determines their imaging characteristics; LMCs follow fat signal on all MR sequences [1, 3]. On T1-weighted sequences, a characteristic homogeneous hyper-dense lesion can be seen occupying variable lengths and extents of the distal spinal canal and soft tissue space. Sagittal images are particularly useful for defining the rostral-caudal extent of the lesion and the entry region into the conus [30]. Important details that affect surgical planning

include the lateral extent of the lesion and the relationship of the LMC to the conus medullaris and exiting lumbosacral nerve roots. Another important contribution of MRI is to define coexisting anomalies such as split cord malformations (SCM). Some centers have advocated constructive interference in steady state (CISS) imaging to define critical interfaces with normal tissue in order to facilitate surgical dissection [42].

CT

CT scans are of limited value for assessing LMCs other than to detail the surrounding bone. CT myelography has largely been replaced by MRI for defining the important interfaces between fat and exiting nerve roots and the conus.

Classification

Three different classification systems have been widely used over the past 25 years.

Chapman defined three types of lipomyelomeningocele: dorsal, caudal, and transitional. Later refinements defined subgroups but the three-category classification has dominated practical clinical use. In a dorsal LMC the fatty-fibrous mass extends directly from the subcutaneous region through a dural defect to attach to the dorsal surface of the conus [10]. Characteristically, these are the most focal attachments with the least involvement of exiting nerve roots. Dorsal LMCs can also be smaller and more fusiform overall than other LMCs. In a caudal LMC, there is a similar dural defect and replacement with fatty-fibrous tissue, but the connection is at the most caudal extent of the conus. Because the exiting nerve roots are caudally directed, they are typically densely involved in the fatty mass. A transitional LMC approaches both dorsally and caudally and densely invades the central canal of the conus [10]. These are therefore the most challenging lesions in respect of defining the planes separating them from normal tissue.

Arai et al. modified the classification scheme popularized by Chapman and added more categories. In addition to dorsal, caudal, and transitional, the Arai scheme combines lipomas of the filum and differentiates between lipomas (dorsal, caudal, transitional) and lipomyelomeningoceles [7, 12]. Therefore, five types of lipoma are distinguished in this classification system, which is reportedly widely used in Japan and Asia. Lipomas of the filum are not included in other classification systems because they are anatomically and surgically different from conus lipomas. The key distinction here is the existence of a subcutaneous cystic meningeal sac into which the distal spinal cord and conus directly project [7, 12].

On the basis of surgical observation and adaptation of technique, Pang refined the classification into dorsal, transitional, and chaotic [8, 17, 43, 44]. Dorsal lipomas are characterized by a lipoma-cord interface that is solely on the dorsal surface of the cord and spares the conus. Nerve roots are therefore never incorporated in a dorsal lipoma. A critical distinction in this classification system was the

definition of the fusion line as the demarcation between the lipoma and the cord and pia [8]. Identification of this crucial oval line (always observed just medial to the dorsal root entry zone and exiting nerve roots) is central to the pursuit of radical resection. Transitional lipomas show a rostral end identical to dorsal lipomas (no nerve roots, fusion line) but a caudal end that involves and invades the conus medullaris at a tangential angle. The lipoma-cord interface is therefore more complex and varied in its interface [8, 44]. The lipoma is sometimes asymmetric and the cord rotated and asymmetric. Two relationships remain unchanged and are important for identifying dissection planes [8, 44]. First, all neural tissue remains ventral to the lipoma. Second, the fusion line is always immediately medial to the DREZ and entering sensory nerve roots. Embryologically, dorsal and transitional lipomas are best considered defects of primary neurulation. Several molecular explanations have been proposed, but the most widely accepted one hypothesizes that focal premature disjunction allows paraxial mesodermal tissue (fat and fibrotic tissue precursors) to bypass the open neural folds and invade the central canal [43–45]. Chaotic lipomas are characterized by an anatomical disorder that according to Pang reflects an early defect in secondary neurulation. This hypothesis holds that lipogenic progenitor cells become surrounded and embedded by condensing neural cells of the caudal cell mass during aberrant secondary neurulation. The lipoma-cord interface is not discrete and is typically hard to discern [8, 43, 44]. The typical chaotic interface of fat and neural tissue makes dissection and removal very difficult. Resection of chaotic lipomas is guided by real-time intraoperative electrophysiological monitoring rather than visual planes and proprioception. Fortunately, chaotic LMCs are uncommon and are often associated with caudal agenesis [44].

Evolution of Surgical Approaches

The modern controversy surrounding the management of LMCs can be elucidated by understanding the evolution of concepts and approaches over the last 25–40 years. From antiquity to the beginning of the modern era (mid-twentieth century), there were limited understanding of all forms of dysraphism and no serious surgical attempts to disrupt their pathophysiology (see Chap. 1). The standard practice for lipomas at that time was a superficial debulking procedure that never addressed the intraspinal pathology. Prior to the 1960s, patients with all forms of dysraphism were treated conservatively and not operated upon [1, 9]. The 1970s brought about a fundamental change in the overall approach to various forms of spina bifida [38]. The historical context is important in shaping the approach to occult forms of dysraphism such as LMCs [1, 3].

During the mid-1940s and 1950s, it had been observed that patients with occult dysraphism demonstrated progressive neurological decline. Bassett was the first to propose that the neurological deficit associated with spinal lipomas was due to tethering and traction [29]. The development of CT imaging during the 1980s and the development and widespread use of MR imaging in the 1990s enabled visualization of the structures involved to be improved.

Preliminary favorable results of surgical untethering gave rise to an assertive approach predicated upon the concept that most patients harboring LMCs were neurologically normal at birth and demonstrated progressively worse neurological capability over time. Many series from this era attest to low rates of neurological impairment in young patients with LMCs. Byrne et al. reviewed a large cohort in Chicago and concluded that untethering virtually always led to improvement [13]. Several papers also demonstrated that patients who had become symptomatic did comparatively poorly with untethering surgery [12, 18, 32, 36, 46]. Kanev and Bierbrauer found that 37% of patients had normal neurologic exams upon first examination but normal findings in unoperated children decreased logarithmically with time [6]. The central concepts of this group of studies were that TCS is predictable, progressive, and central to neurological decline and that carefully conducted surgery could prevent this otherwise inevitable, frequently painful, irreversible decline. The practical approaches that emerged were (a) surgical untethering for the symptomatic patient with a conus lipoma and progressive neurological decline and (b) prophylactic untethering for asymptomatic patients. These concepts became widely accepted and practiced.

The methodology in these studies was not rigorous by contemporary standards. Virtually all were observational single-institution cohorts with non-standardized, non-validated data points collected retrospectively from medical records by the surgical team and as such were susceptible to bias. Only a limited number of clinical series clearly documented the progression of neurological deficit before surgical intervention [22]. None acknowledged or controlled for the possibility of symptomatic emergence in older children rather than disease progression.

Young children were frequently said never to be affected despite methodological difficulties in refined assessment of sphincteric and lower extremity function in very young children. Furthermore, older asymptomatic children who were never treated were also not considered in the analyses of natural history arising from outcome studies of early-treated patients. This important omission impeded accurate assessment of the effectiveness of prophylactic surgery [21–23].

Perhaps more importantly, the cohorts of patients who underwent surgery for prophylactic untethering demonstrated significant recurrence of neurological decline over time. Several published series documented neurological deterioration in previously asymptomatic patients who were subjected to early prophylactic surgery [2, 19, 37, 47–50]. The group from the Necker-Enfants Malades Hospital in Paris initially embraced aggressive prophylaxis but found that 60% of patients who underwent prophylactic untethering demonstrated neurological decline within 12 years [37]. Actuarial risks of progressive neurological decline were reported as 20–70% at 8–9 years from multiple experienced centers despite early prophylactic surgery [22, 40, 50, 51]. Goodrich and colleagues performed a meta-analysis that incorporated 608 patients reported in the literature and found that the longer the follow-up, the greater the incidence of neurological decline [49]. They found a linear relationship following TSCR for LMC between (a) time between untethering and recurrence of symptoms and (b) an approximately 3.3% increase in incidence per year [49]. This cast doubt on the power of prophylactic untethering to prevent decline and change the natural history of the condition.

During this period, surgical investigators from disparate geographical locations began to question some of the fundamental assertions of the classic approach. Several looked closely at cohorts of children harboring LMCs in their own centers and found that many were neurologically impaired early in life [7, 21, 22]. Further, some irreversible iatrogenic injuries were evident [27, 36, 51, 52]. Wound-related complication rates were also noted to be significant (10–25%), and neurological injury was perhaps more common than previously reported [1, 3, 52]. These observations, coupled with a realistic awareness that the natural history of LMC had never been directly demonstrated but rather inferred, led to reconsideration and an evolution of operative approach toward a more conservative route in many centers. Some centers began simply to follow patients and concluded from observing those who were not operated that the natural history is more benign in some patients with LMC [21–23]. No experienced center denied that a significant percentage of patients harboring LMCs showed neurological decline, but the universality of the finding of decline was questioned, and a policy of close observation until decline was observed was advocated. One of the most influential of these was the group in Paris. This center published early studies advocating conventional classic principles, but came to take a more conservative approach as time and experience grew [37, 53]. With time, Pierre Kahn became one of the leading advocates of the conservative approach [22]. Centers in Canada and Europe advocated a more conservative operative approach for asymptomatic patients on the basis of reviews of their institutional experience [21–23]. Kulkarni et al. observed a 33% incidence of neurological decline in patients prospectively observed conservatively. This contrasted favorably with the 46% incidence in those treated surgically [22]. However, the surgical group was evaluated retrospectively and the conservative group prospectively. Wykes and colleagues reported that only 5.9% of children with asymptomatic lipomas who were followed closely, clinically, and radiographically (MRI) over the preceding decade at Great Ormond Street Hospital for Children in London demonstrated clinical decline without intervention [23].

During this time, Pang dedicated a significant part of his career in Pittsburgh and Oakland to the study, classification, and surgical treatment of occult dysraphisms including LMCs and came to advocate a fundamentally different policy. Pang originally learned the classical concepts of TSC and embraced the concept that most neurological decline in OSD patients arises progressively. However, the observation that 65% of patients treated with limited resection came back with a recurring decline of neurological function prompted him to consider a different approach [8]. He concluded that partial resection of lipomas promoted morbidity and failed to interrupt the natural history of neurological decline from tethering [8, 43, 44]. In response, he developed a new classification scheme and completely revamped the operative procedure [8]. Beginning in 1991, Pang concluded that partial resection failed to prevent the ominous natural history of the disease reliably and embraced the concept that radical resection of lipomas with meticulous reconstruction of the neural placode resulted in the best long-term outcomes. The cornerstone of his approach lay in meticulous microsurgical dissection of the lipoma, releasing it far laterally and identifying the white fibrous plane that he always observed between

the lipoma and the normal neural tissue. The conceptually simple and appealing but technically challenging goal at the end of radical resection is a small tube in a large reconstructed dural sac. In a sequence of publications, Pang and colleagues summarized the rationale, surgical technique, and results of his undertaking of radical resections of LMCs [8, 17, 43, 44]. He holds that the anatomy is constant within subtypes of lipomas (determined by the type of lipoma – dorsal, transitional, or chaotic) and that the plane between the lipoma and the neural placode is nearly always discernable and dissectible with proper awareness of the pathological anatomy, technique, patience, and fortitude. Radical resection of fat and expansion of the sac to attain a low cord-sac ratio are the central ideas that prevent recurrent tethering. The cohorts have been followed longitudinally with updates in progress, and adaptations of the technique have been developed. Some reports have matched patients who have undergone radical resection with those observed conservatively to demonstrate the superiority of radical techniques.

Despite excellent results, Pang's techniques appear elusive to many pediatric neurosurgeons. Pang's radical resection procedures are long and exacting and demand the highest standards in technique, endurance, concentration, and intraoperative physiological monitoring (IOPM). Pang alludes to the difficulty and challenge of these cases in his references to "long hours of repetitive micromotions," "incising endless adhesions perilously close to the spinal cord," and "working against physical exhaustion, dissolving concentration, and grueling monotony." Some tools are not commercially available. Several senior surgeon leaders in dysraphism have directly counselled against aggressive resection at the lipoma-cord interface owing to the risk of neurological injury [21, 41]. Other surgical teams have great IOPM, extensive surgical experience, and abundant stamina yet do not readily or uniformly locate and follow the white fibrous plane that is the key to radical dissection. Perhaps most importantly, there is a perception and cultural undercurrent that some surgeons who have attempted radical resection have been surgically "lost" or struggled to preserve the location of the white plane or have injured the patients. Many surgeons perform aggressive resection and reduce the mass of the lipoma "as much as possible" but deliberately leave a layer of fat rolled up within the reconstructed tube. Other centers where Pang's trainees have practiced have alluded to a preference for radical resection and optimization of the sac-canal ratio, but there are very few comprehensive series in which the radical resection techniques pioneered and advocated by Pang have been reported. Pang claims that the techniques can be mastered by any neurosurgeon willing to take the time and dedication to learn and follow them. At present there is limited reported experience from other centers using these techniques.

Talamonti and colleagues, who embrace radical resection and small cord-sac ratios, have recently reported a limited cohort of patients where both options were presented in detail to families. In this single-center series of 56 asymptomatic patients, 32 underwent surgical treatment, and 24 were observed. At a mean follow-up of 9.7 years, there were clinical signs of tethered cord in 10% of the observed patients and 29% of those who were observed nonoperatively. Statistical significance was approached but not reached owing to the limited size of the cohort [51].

Surgical Techniques

Conventional Resection/Untethering ("as Much as Possible") of Spinal Lipomas

The patient is placed under general anesthesia and is positioned prone. The anesthetic strategy is planned with the anesthesiologist to optimize intraoperative nerve monitoring. Intramuscular needle electrodes are placed in the rectum, urethral sphincter, and representative muscles of the lower extremities to enable motor-evoked potentials, EMG, and somatosensory-evoked potentials to be monitored continuously. A MRI scan in the sagittal plane defines the rostral-caudal extent of the lipoma. An incision is planned directly through the fatty mass directly on the midline. Intravenous antibiotics are administered before incision, and the skin is prepped with a preferred antiseptic solution. After sterile drapes are used to fashion a field and after a surgical time out is performed, the incision is made. The lipoma is divided and the subcutaneous portion is not removed. We value the effect of the residual subcutaneous fatty mass in preventing a dead space that could otherwise fill with CSF and threaten good wound healing. The normal rostral thoracolumbar fascia is exposed, and self-retraining retractors are placed to facilitate exposure. The defect in the fascia is typically readily evident, and the stalk of the lipoma is often discrete and quite evident. We prefer to gain epidural access by removing the last normal lamina and defining a normal dural plane there.

Once the normal dural plane is exposed, the dura is opened on the midline rostral to the lipoma, and opening continues until the portion of the lipoma that perforates the dura is encountered. The key interface to define is between the junction of the lipoma with the spinal cord complex and the dural relationship. All functional nerve roots are ventral, the sensory ones lateral and the motor ones mostly medial. The junctional zone is sharply developed in an oval fashion at the interface of the dura and the lipoma. A purely dorsal lipoma can be dissected free of the subcutaneous component at that point resulting in a flat open surface of fat within the substance of the cord and a disconnected portion of subcutaneous lipoma. Some surgeons advocate use of the laser at this point to reduce the bulk of fat maximally within the substance of the conus. We prefer the ultrasonic aspirator to debulk the intramedullary component of the lipoma and have traditionally not attempted to define the interface between the lipoma and the conus aggressively. We reduce the fat as much as possible without intrusion beyond a fatty layer and then reconstitute the neural tube by rolling it up. It is important to find and section the filum terminale in dorsal lipomas as they can be a source of persistent tethering.

A caudal lipoma exits the conus inferiorly in the same axis as the exiting nerve roots. The conus becomes progressively larger caudally owing to lipoma infiltration, and the lipoma often invades asymmetrically, resulting in rotation of the cord and lipoma. Lateral dissection commences along the interface between the dura and lipoma as the conus thickens to liberate it. Dorsal projecting nerve roots are typically nonfunctional and can be divided after stimulating them with an intraoperative probe to ensure they are nonfunctional. The central intramedullary portion of the

lipoma can be reduced with a laser or cavitron, but it is more difficult to form a caudal lipoma into a tubular structure.

Transitional lipomas share features of each of the other types. The dural attachment becomes progressively more ventral as dissection commences caudally. Viable nerve roots exit through the lipoma, and intraoperative monitoring is valuable for discerning functional nerve roots. Traditionally, a maximal "safe" resection is performed, and the dura is expanded with dural grafts or autogenous (harvested fascia lata) grafts to make the closure both watertight and capacious.

Total/Near Total Resection of Spinal Cord Lipomas with Neural Placode Reconstruction (Pang)

Five steps define the complete resection technique, which is conceptually similar yet radically more aggressive than the traditional approach [8, 17, 43, 44].

The first step is exposure, which involves a midline incision with preservation of the subcutaneous lipoma and exposure of the epidural space of the most caudal intact lamina. A key step here is wide laminectomy of the involved level to facilitate lateral visualization of the insertion point of the lipoma. The lipoma and cord are fixated laterally like a hammock over the ventral space that contains CSF, and exposure and access to these regions are central to the release needed for liberating the lipoma [8, 17, 43, 44].

The second step is detachment of the lipoma from the dura [8, 17, 43, 44]. This involves rostral opening followed by taut retraction of the opened dural margins to ensure full exposure of the lateral aspects of the canal where the lateral extent of the lipoma attaches to the dura. Pang colorfully and perhaps indelicately labels this key step "crotch dissection" to emphasize the dynamic medial retraction of the lipoma to facilitate exposure and dissection within the junction of the lateral lipoma and the dura. This step is crucial for releasing the lipoma across a transverse line that connects the lateral points of fixation where the lipoma and cord are suspended like a hammock. This step is meticulously carried out caudally and bilaterally to release the lipoma from its suspending insertion, and it descends into the anterior, ventral CSF-containing space.

The third step involves resection of the lipoma [8, 17, 43, 44]. This dissection commences at the rostral extent of the exposure and is initiated at the dorsal root entry zone (DREZ). In this location, sharp dissection techniques define the interface between cord and lipoma and result in the exposure of the "white plane" that forms the interface between cord and lipoma. Other experienced neurosurgeons attest to the existence of this plane but are less convinced of its surgical value because of its inconsistency and variability. These surgeons counsel against aggressive surgical dissection in the plane between lipoma and cord. Pang advocates sharp microdissection to define the white plane across its entire extent and avidly warns against use of the laser, which burns and fuses tissue planes rather than defining them. The fusion line is the crucial interface between the lipoma and cord face that is reliably located immediately medial to the dorsal root entry zone. If all dissection is conducted medial to the fusion line, then extensive dissection along the white plane can be

pursued with minimal risk. This is simplest in a dorsal lipoma, where the plane is linear and flat. In transitional lipomas it always sweeps ventrally and often is rotated, making pursuit of the white plane more difficult. Planes are defined by monitoring and electrophysiology in chaotic lipomas. Fat resection continues slowly, deliberately, and methodically until gross total resection of all visible fat is accomplished.

The fourth step is neurulation of the placode [8, 17, 43, 44]. Once fat is removed, the tubular shape is reestablished by sewing together the pias of each side along the dorsal surface with very fine (8-0 PDS) sutures. The principal advantage of this is to ensure a pial surface toward the dura and thus reduce the likelihood of tethering.

The fifth and final step incorporates an elastic dural graft patch to ensure the dural sac is capacious [8, 17, 43, 44]. Post hoc multi-regression analysis of Pang's series demonstrates that this step is perhaps the most important. Of all factors assessed, a postoperative sac-to-canal ratio of less than 0.3 was the single most important for predicting excellent long-term outcome and freedom from tethering. If the cord-sac ratio was below 0.3, the progression-free survival (PFS) exceeded 96%, but if it exceeded 0.5, then the PFS decreased to 80.6%.

These techniques have generated a progression-free survival rate of 82.8% at 16 years. The results are especially favorable in previously unoperated cases, in which the PFS exceeded 98% at 16 years [17, 43, 44].

Surgical Outcomes and Complications

Conventional Techniques

As with many time-dependent outcomes, there is no simple summary way to express surgical outcome properly. Most series are retrospective, single institution, and report rates of cessation, stabilization, or improvement of neurological decline that that vary widely (40–95%) but center on the 80% range. Direct neurological injury appears increasingly rare and is reported at 5–8%. Wound issues are probably underreported at 10–12%. Delayed re-tethering is a real risk, and it is critical to continue to follow and assess patients longitudinally, particularly during the first two decades of life. Urological outcomes are variable and remain controversial [21, 45, 49, 54]. Patients with normal voiding and urodynamics prior to surgery appear at limited surgical risk with simple lipomas but increasing risk with the degree of LMC complexity. Children and patients with minimal voiding dysfunction appear to show better response to untethering than older patients with more severe voiding and urodynamic dysfunction. Close urologic follow-up and individualization of care are recommended [45, 54].

Radical Resection

The 20-year PFS of patients treated with radical resection and reconstruction of the dura is 88% for all lipomas and greater than 98% for previously unoperated

lipomas. If the lipoma is only partially resected, then the PFS is 35% at 10.5 years. A low cord-sac ratio is the only variable that predicts good outcome in multivariate regression analysis.

Alternative Procedures

Dissatisfaction with outcomes and complications related to direct spinal cord untethering for TCS has recently prompted some surgeon investigators to consider novel techniques to manage progressive tethered cords associated with LMCs.

Subtraction Osteotomy

This technique involves vertebral column shortening via pedicle or vertebral body dissection to accomplish 15–20 mm of spinal column shortening coupled with instrumented fusion. In preliminary series at experienced pediatric spine centers, subtraction osteotomy appeared safe and acutely effective, but there are few available data on safety, longitudinal effectiveness, and consistency of effect in larger cohorts of patients with TSC.

Endoscopic Resection of Lipomas

Endoscopic lipoma resection has been described in small series of filum lipomas but has no current role in the more complex lipomas of the conus and spinal cord.

Conclusions

Lipomyelomeningoceles are complex congenital anomalies that show extraordinary variability in their anatomy. The underlying degree of neurological insult arising from developmentally disordered neuroanatomy also varies and is probably underappreciated and underrepresented in surgical studies. As such, the definition of symptoms has evolved and the semantics are important. A contemporary definition of symptomatology must incorporate a longitudinal, temporal view that demonstrates decline in function rather than the clinical emergence of a preexisting neurological deficit. Fundamentally, the challenge in surgical approach comes from the root of the problem.

However, it is also clear that the natural history is ominous in most patients. Tethering promotes decline over time, and well-planned and well-executed surgery can interrupt the decline. Patients with a LMC who demonstrate progression in symptoms should undergo cord untethering with INMC. Asymptomatic patients remain controversial; however, all series that have observed treated and untreated patients concomitantly have demonstrated greater decline in the untreated cohorts.

Decline can be at least temporarily arrested by surgical intervention and untethering, and risks of surgery for direct neurological injury are low for simple lesions but escalate with increasing LMC complexity. Many of these patients show later decline, and all need to be carefully followed.

In practical, realistic terms, the results of radical resection and reconstruction advocated by Pang represent an unattainable goal for many pediatric neurosurgeons. Many dedicated, fine surgeons who practice at well-recognized centers of excellence with state-of-the-art equipment cannot or do not reliably find the planes and are legitimately concerned about causing injury while treating a condition for which the natural history is incompletely understood. Perhaps radical resection is the ultimate and ideal treatment. Pang has clearly detailed the techniques and outcomes from his personal series. However, until other surgeons and authors replicate and present similar series more widely, it remains an ideal that is not universally available. Pang has trained fellows in the technique for decades, but the literature describes few significant cohorts from other centers showing the benefit of radical resection. Whether others can replicate the admirable results and safety record of Pang over time remains to be seen.

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Split Cord Malformations

12

Brandon G. Rocque

Introduction

Split cord malformations (SCM) are abnormalities of the spinal cord, ranging in severity from the very simple to profoundly complex. Their presentation can be completely occult, or they can present with some of the most obviously abnormal cutaneous findings. Von Recklinghausen described a case of SCM in his classic *Studies on Spina Bifida* in 1886 [1]. Herein, he posited that the mythological creature the satyr may have its origins in the SCM. The hairy patch or hypertrichosis that often accompanies these lesions served as the "tail." Because of the neurological changes that result from spinal cord tethering, an individual with SCM may have clubbing of the feet, thus appearing to have a "cloven" foot. The resulting constellation could very well have been the basis for the satyr myth.

The term "diastematomyelia," meaning cleft spinal cord, was introduced in 1837 in an autopsy report [2]. Decades later in 1892, Oscar Hertwig used that term to describe a spinal cord split by a midline structure, with the two parts of the split cord each contained within their own dural sleeve. He distinguished this from diplomyelia, meaning "double spinal cord," a term he used to describe a SCM contained within a single dural sleeve [2]. In the 1990s Dachling Pang advanced the understanding of the SCM markedly, providing a unified theory of embryology and simplifying terminology.

In this chapter, the classification and terminology for the SCM will be reviewed. Additionally, the proposed embryology, natural history of untreated SCM, and the surgical technique for their operative treatment will be discussed.

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Anatomy and Classification

Historically, SCM were classified as two distinct pathological entities, thought to arise from different embryologic aberrancies. Those malformations with a midline septum separating the halves of the split cord were referred to as diastematomyelia. Malformations in which the two halves of the cord were enveloped within a single dural sleeve were referred to as diplomyelia. As we will discuss below, the prevailing theory of pathogenesis prior to the end of the last century posited distinct mechanisms for the occurrence of these two types of SCM.

In the early 1990s, Pang suggested renaming these entities using the terms "SCM, types 1 and 2" [3]. Type 1 SCM are those that were previously known as diastematomyelia, characterized by a bony or cartilaginous septum between the hemicords, with each hemicord contained in its own dural sleeve. Type 2 SCM, formerly diplomyelia, are those in which both hemicords are contained within a common dural sleeve. Most neurosurgeons currently use SCM type 1 and type 2 for both clinical and academic descriptions, though both diastematomyelia and diplomyelia are still in somewhat common use.

Type 1 SCM are characterized by the presence of two distinct dural sleeves (Fig. 12.1). Each portion of the split spinal cord is contained in its own dural compartment. Between the dural sleeves, there is nearly always a septum, composed of connective tissue, most commonly bone, but sometimes cartilage. Often the septum contains other connective tissue elements as well, including blood vessels. Arteries in the septum can be quite robust and can cause challenges during surgical resection.

While the septum of a type 1 SCM is most commonly in the midline, it can also occur at oblique angles and with substantial asymmetry. If the original embryologic insult leads to asymmetric division of the spinal cord, one hemicord may be substantially larger than the other. In these cases, the dural sleeve and bony canal will be asymmetric as well (Fig. 12.2). In extreme cases, the septum may be oriented in

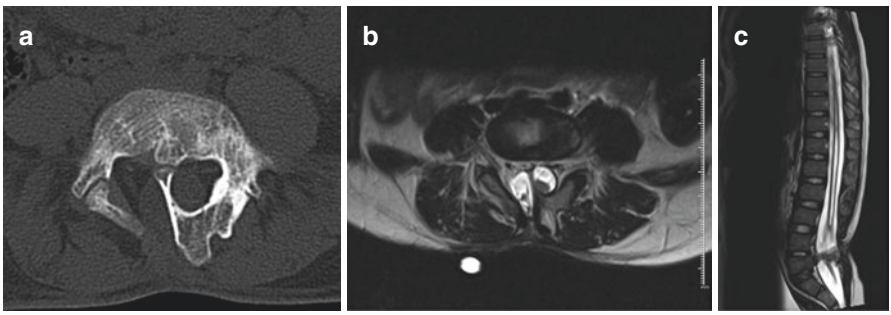

Fig. 12.1 Example of a type 1 SCM. Panel (**a**) is an axial CT scan showing the bony septum between two hemicords. Panel (**b**) is an axial T2-weighted MRI scan showing the CSF space and nervous tissue. Note that in this case, the two hemicords are asymmetric in size. Panel (**c**) shows a midsagittal T2 MRI scan, at the level of the bony septum. The spinal cord proximal to the split demonstrates syringomyelia

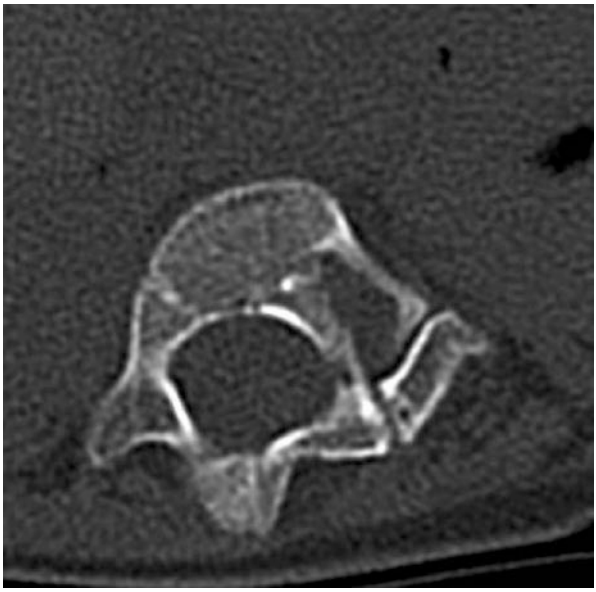

Fig. 12.2 Axial CT scan shows a type 1 SCM with asymmetry

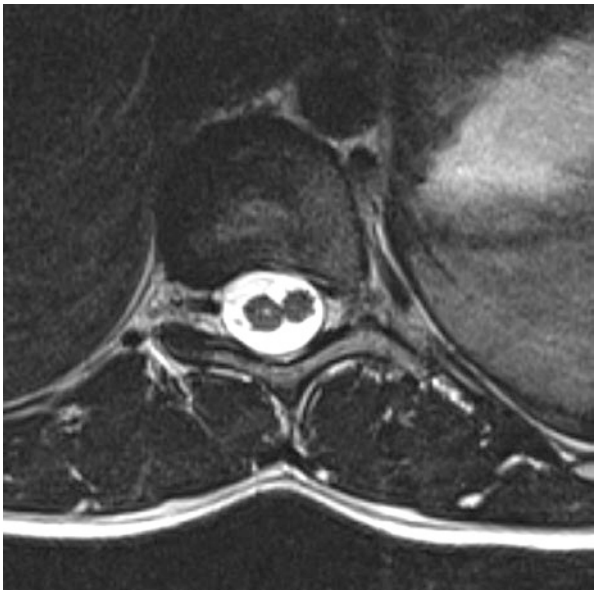

Fig. 12.3 Axial T2-weighted MRI showing a type 2 SCM. Both hemicords are contained within one dural sleeve. Note that there is essentially no space between the hemicords

the coronal plane, perpendicular to the usual midline position. This likely develops due to rotation of the spine after the initial embryologic insult.

In type 2 SCM, the two hemicords are contained within a single dural sleeve (Fig. 12.3). While there is no midline septum, there are intradural tethering bands, most commonly extending from the medial surface of each hemicord, and attaching

to the dorsal or ventral dura mater. The highest proportion of these bands tend to cluster at the distal end of the split, near where the two hemicords reunite [4].

Cutaneous Stigmata and Associated Conditions

The presence of occult spinal dysraphism is often heralded by a cutaneous sign. In the case of SCM, there are many cutaneous stigmata that may be associated. The classic example of which is focal hypertrichosis (focal hirsutism), or the hairy patch. Focal hypertrichosis is present in a little over 50% of reported cases of SCM, and it is more common with type 1 malformations than with type 2 [4–6]. The hair of the hairy patch is typically thick and stiff, often described as truly hirsute, as compared to typical infant body hair, which can sometimes be slightly thicker over the lumbar spine. The hairy patch associated with SCM is usually not a subtle finding.

Also, commonly seen with underlying SCM is the cutaneous hemangioma. Present in about 50% of cases, it often underlies the focal hypertrichosis and thus is not the feature that immediately draws attention [4]. Other cutaneous signs of dysraphism are seen with less frequency: a sacral dimple or dermal sinus has been reported in 12% and an abnormal gluteal cleft in 8% [4, 7]. Rarely, SCM may be associated with a caudal appendage or "human tail" [8, 9].

The complexity of a SCM varies from minimal hemicord separation to extremely complex abnormalities. Similarly, there are a wide variety of other embryologic abnormalities that may be coincident with SCM. These are sometimes seen in conjunction with typical cutaneous signs. A *form fruste* of SCM is the split filum terminale. Here the spinal cord may be normal, with only the filum terminale duplicated (Fig. 12.4). This comes to medical attention because of other associated findings, such as a dermal sinus tract or spinal lipoma [10].

Essentially any type of spinal dysraphism can occur in one hemicord of a SCM, sparing the other hemicord. The most extreme example of this is hemimyelomeningocele. In this condition, one of the hemicords continues to a normal conus medullaris, while the other ends in an open myelomeningocele defect [11, 12]. There is usually pronounced asymmetry in neurological function of the legs, as expected.

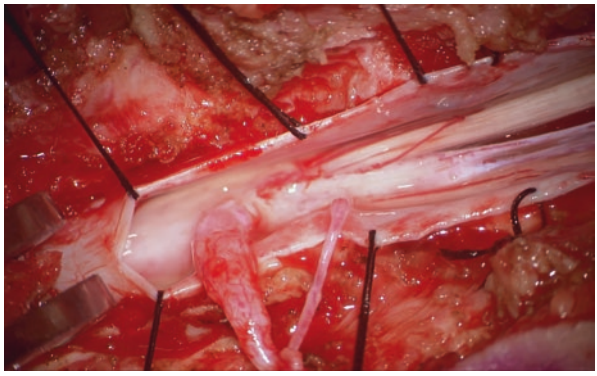

Fig. 12.4 Intraoperative photograph of a duplicated or "split" filum terminale. On the right side of the image, the duplicated filum is visible. On the left, the dermoid and dermal sinus tract are seen. This individual presented with a lumbar dimple

Similarly, SCM may occur in infants thought to have only myelomeningocele. It has been reported that 6% of infants with myelomeningocele may also have a SCM, often identifiable by an area of hypertrichosis immediately rostral to the myelomeningocele defect or because of evidence of a midline bony septum identifiable on radiograph [13].

Dermoid cysts, spinal lipoma/lipomyelomeningocele, neurenteric cysts, and spinal teratomas have all been reported to occur in conjunction with SCM as well [4, 14]. The typical cutaneous stigmata of these lesions, such as subcutaneous lipoma in conjunction with lipomyelomeningocele or a sacral dimple in conjunction with a dermal sinus tract, may be present with or without accompanying hypertrichosis. Clinicians should be alert to the possibility of SCM in addition to other dysraphism when hypertrichosis is present along with other stigmata and when there is asymmetry of neurologic function in the legs.

Deformities of the bony spine can also be found in association with SCM. The embryologic insult that results in SCM malformations can also be associated with hemivertebrae, block vertebrae, missing laminae, or other abnormalities of the skeleton [15]. Scoliosis can be seen in association with SCM and may be the presenting sign in an otherwise asymptomatic individual. Traditional neurosurgical practice dictates that surgical repair and untethering of the SCM should be performed prior to surgical correction of the scoliosis to prevent neurologic decline. However, a prospective, single-institution cohort study of 214 individuals with scoliosis and SCM showed no permanent neurological decline after scoliosis correction, despite not first treating the SCM [16].

Proposed Embryology of Split Cord Malformations

Prior to the unified theory of embryology proposed by Pang in 1992, the prevailing notion in the literature was that type 1 and type 2 malformations arose from two distinct embryologic mechanisms. Diastematomyelia (two distinct dural sleeves) was thought to occur because of invasion of the neural tube by mesenchymal tissue, while diplomyelia occurred from focal twinning of the spinal cord. Pang's unified theory posits that these two different types of malformation arise from a common embryologic insult.

During the second and third week of human embryologic development, the embryo has undergone gastrulation, becoming trilaminar after migration of cells that will become mesoderm between the epiblast and the hypoblast. The notochordal process then elongates between the epiblast and hypoblast, starting as a canal with communication to the amnion through the primitive pit. During the 3rd week, the canalized notochord fuses with the underlying endoderm to form the primitive neurenteric canal. After a few days, this communication closes, and there is no longer any connection between the amnion and the yolk sac.

The key event in the development of the SCM is the persistence of an accessory neurenteric canal after the closure of the primitive neurenteric canal. This connection between endoderm and ectoderm by definition must split the notochord and

thus split the tissue that will develop into the spinal cord. In this theory, the degree to which the persistent canal "heals" and the presence of mesenchymal tissue within the accessory canal determine the severity of the split cord. If there is no migration of mesoderm into the accessory neurenteric canal, the result is a type 2 split cord, where the two hemicords are contained within one dural sleeve. When mesenchyme is present, it then develops into the dual dural sleeves and the bony or cartilaginous septum of the type 1 split cord. The septum can therefore contain any tissues derived from mesoderm, such as fat or blood vessels.

This unified theory of embryogenesis has been tested in an animal model, in which induction of a fistula between amnion and yolk sac in amphibian embryos induced SCM [17]. In addition, according to Pang, it explains the wide spectrum of pathology that makes up the SCM [3].

Natural History

Definitive assessment of the natural history of SCM is challenging, since there are no large-scale natural history studies. However, it has been observed that most children with SCM have normal or nearly normal neurological function at birth, the notable exception to this being children who are born with obvious additional pathology such as hemimyelomeningocele [4, 15]. However, adults with SCM typically exhibit findings that are likely attributable to long-standing spinal cord tethering, such as neurogenic bladder or lower extremity weakness. Put another way, children with SCM may be more likely to come to medical attention because of a cutaneous finding, whereas older patients may be more likely to present with slowly progressive neurological deficits, orthopedic conditions, or pain [18]. There have been reports of rapid decline after sports injuries, particularly when the injury involves flexion of the spine; however, functional decline due to SCM is most often insidious [15]. The current consensus opinion is that an individual with a SCM is at risk for neurological decline over time and that the risks of treatment should be weighed against this potential for decline.

The presenting feature for SCM is usually either a cutaneous abnormality or neurologic decline [18]. Sometimes the orthopedic consequences of neurologic decline are apparent as well, including pes cavus, hammer toes, equinovarus deformities, and scoliosis. Scoliosis associated with SCM can be either a consequence of neurologic dysfunction, or it can be a fixed deformity resulting from bony abnormalities that are associated with SCM, such as butterfly vertebrae or hemivertebrae. In adults, back pain is a common feature of untreated SCM. However, in children this is less common, with pain as one of the presenting complaints in only about one third of children.

Historically, it was thought that type 2 SCM, with both hemicords contained within the same dural sleeve, were less likely to lead to progressive neurological decline. However, like type 1 SCM, type 2 typically have abnormal medially directed nerve roots or fibrous connections to the dura that can act as tethering lesions. Therefore, it is thought that both type 1 and 2 SCM have an unfavorable natural history and, in most cases, warrant surgical treatment.

Treatment

Preoperative Workup

Preoperative workup of the SCM patient includes a complete neurological examination, with particular attention paid to sensory and motor deficits. In addition, a urologic examination is performed in most cases, including urodynamic studies to document the function of the bladder prior to operative treatment. Plain X-rays can be obtained to evaluate for scoliosis. CT scan may be useful to reveal the details of bony anatomy. In particular, a CT myelogram may be useful to demonstrate the relationship between bony septum and neural elements. MRI scan will show nervous tissue, the extent of the split cord, and may show subtle tethering bands.

Indications for Surgery

As noted above, the natural history of SCM is thought to be insidious progression of neurologic deficit. Therefore, the presence of SCM alone is indication for treatment in most cases. The goal of surgery is complete untethering of all spinal elements. This includes removal of the midline septum in type 1 malformations, removal of intradural tethering bands, both dorsal and ventral to the spinal hemicords, and sectioning of the filum terminale [19]. Surgical technique for type 1 and type 2 malformations differs slightly.

Type I SCM Surgical Technique

After exposure of the bony elements, a laminectomy is performed first above and below the split cord and finally over the midline spur. The spur is then left as an island of bone between the two dural sleeves. The surgeon then dissects the bony spur free from the medial aspects of the dura. This may be particularly challenging when the midline spur is oblique in orientation. In addition, the midline spur sometimes contains blood vessels which can bleed substantially. The surgeon must take care to control these well during removal of the spur.

Once the spur is removed, the dura is opened above and below the SCM and then along each hemicord. All medially projecting attachments from the two hemicords to the midline dura must be sharply cut. These may have the appearance of nerve roots, but they are not functioning neurologic tissue, and they may be sacrificed without deficit. Any projection from the medial aspect of the SCM should be treated as a potentially tethering lesion.

After both hemicords are completely disconnected, the medial dura is resected flush with the dorsal aspect of the vertebral body. No effort need be made to close the ventral dura. The dorsal dura is then closed primarily or with a graft to create a single dural sleeve with no intradural tethering points. Fascia and skin closure is performed in the usual fashion. The accompanying video (Video 12.1) depicts the untethering of a type 1 SCM.

Type 2 SCM Surgical Technique

After exposure of the bony elements, laminectomy is performed. Because the SCM is within a single dural sleeve, the location of the split may not be obvious. Therefore, careful localization must be performed with standard techniques. Because there may be tethering bands that traverse the dura and attach to the lamina, care must be taken during laminectomy not to apply traction to these bands. Therefore, it is not advisable to remove multiple lamina in an en bloc manner. In some cases, medially projecting fibers will extend through the dura and terminate on the skin as the so-called meningocele manqué. When such a cutaneous finding is present, localization is easier, as these fibers can be followed from the skin to the level of the split cord.

Dura should be opened slightly off of midline. Once normal-appearing arachnoid and spinal cord are visible, the incision is carried rostral and caudal until a single spinal cord is seen above and below the SCM. At this point it is important to inspect for fibrous bands that project from the medial aspect of the split, as these will act as tethering bands. In a study of 52 patients with type 2 SCM, 21% were found to have ventral tethering bands. Furthermore, in the majority of cases, these bands are not apparent on preoperative imaging studies [20]. Fibrous bands are most commonly encountered at the caudal part of the split. If both dorsal and ventral bands are identified and cut, there is no need to explore the interval between the hemicords. This space is often quite small, and attempt to explore it may put one or both hemicords at risk for injury. After careful dissection of all bands both ventral and dorsal to the split, the dura can be closed primarily.

In both type 1 and type 2 malformations, secondary tethering lesions are frequently present. The most common of these is a thickened or fatty filum terminale. It is important to address all potentially tethering pathology. Sometimes, this can be done through the primary incision. However, in other cases, it may be necessary to make a separate incision to section the filum. Any associated lipoma, dermal sinus tract, or fibrovascular tract should be addressed at the time of SCM surgery.

Outcomes

In simple type 1 malformations and most type 2 malformations, surgical morbidity is low. More complicated lesions, in particular those with obliquity or asymmetry, or those associated with a spinal cord lipoma, surgical morbidity may be higher. Neurologic deficits that have been present for a long time prior to surgery are unlikely to improve with untethering. However, there are reports of more recent deficits improving somewhat after surgery [21]. Regardless, the goal of surgery should be preservation of neurologic function rather than restoration of function that has been lost.

Published literature evaluating outcomes of SCM surgery consists of single-institution retrospective case series and case reports. In these series, neurologic function after surgery is noted to be stable or improved in the majority of patients

[6, 22, 23]. Among adults with SCM who present with pain, surgical treatment has been reported as satisfactory in relieving back pain and facilitating return to work [24].

Conclusion

SCM range from simple to extremely complex spinal dysraphism. There exists little controversy about surgical management, as it is largely agreed that the natural history is unfavorable and that surgical risks are generally acceptable. Goals of surgical treatment are complete spinal cord untethering, including release of all tethering bands associated with the split cord and tethering points that might exist elsewhere, such as the filum terminale. Outcome from surgical untethering is largely favorable.

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Meningocele Manqué

13

Cameron Schmidt and R. Shane Tubbs

Introduction

In their 1972 landmark publication *Spinal Dysraphism: Spina Bifida Occulta* (SBO), James and Lassman coined the term meningocele manqué (MM) (*manqué* means "that which might have been but was not") to describe the intradural tethering of neural structures by congenital dorsal bands (Figs. 13.1, 13.2, 13.3, 13.4, 13.5, and 13.6) [1, 2]. These bands (Figs. 13.1 and 13.2) were characterized by anomalous nerve roots, dorsal fibrous bands, and dorsal adhesions, which tethered the spinal cord, nerve roots, and/or filum terminale against the inner aspect of the dural sac. Association with atretic meningoceles, and similarities between these bands and the recurrent nerve roots commonly found adhering to the necks of meningocele sacs, led James and Lassman to posit that the bands were vestiges of abortive meningoceles that failed to organize late in embryonic development [1]. On the basis of these conclusions, the term meningocele manqué came to serve as their adequate descriptor; according to the authors, no more appropriate classification or explanation could be found.

However, since its initial characterization, the nature of MM has become less clear, allowing for a broadening of the range of surgical findings that have come to be classified under this heading. More recently, challenges to the traditional definitions of MM have been accompanied by a culling and reclassification of entities within MM. While this evolution has resulted in the appropriate subdivision of embryologically distinct variations, MM proper remains confounded in reports from the medical literature. Given this trend, we herein review MM with the aim of providing clarity to this progressively misunderstood entity.

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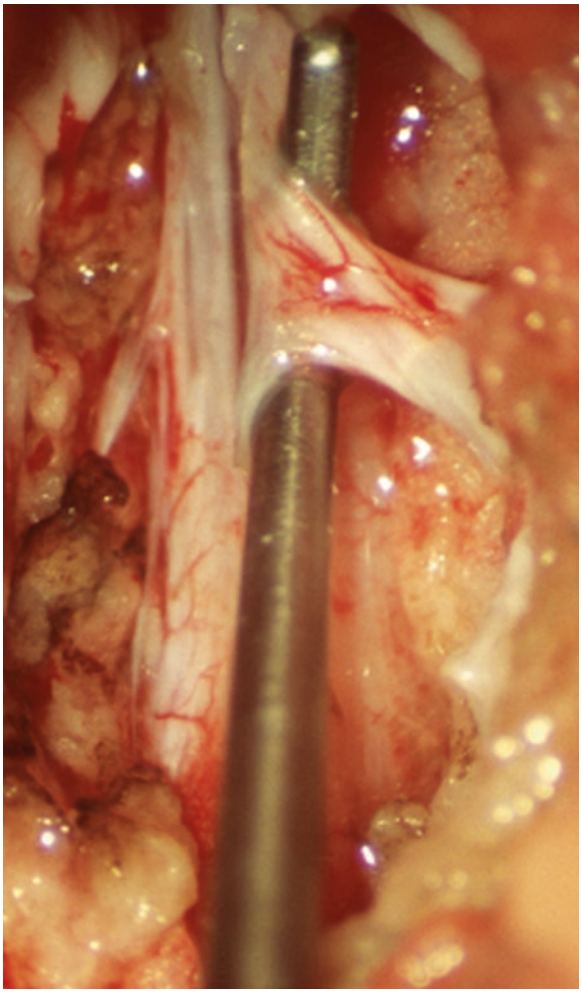

Fig. 13.1 Illustrated intraoperative view of one variety of meningocele manqué

Tethering Tract Characteristics

Per James and Lassman's original definition, MM is characterized by tethering of the spinal cord, nerve roots, and/or filum terminale against the inner dorsal aspect of the dura mater by single and/or multiple aberrant nerve roots, fibrous bands, and/or adhesions [1]. At the points of adhesion, nerve roots and dorsal bands are often twisted and loop in a cranial direction before rejoining normally coursing nerves [2]. Other nerve roots and dorsal bands are simply diverted from their standard course. In most cases the effects of the tethering bands can be appreciated either intraoperatively or radiologically by the dorsal displacement of the spinal cord, cauda equina, or filum terminale.

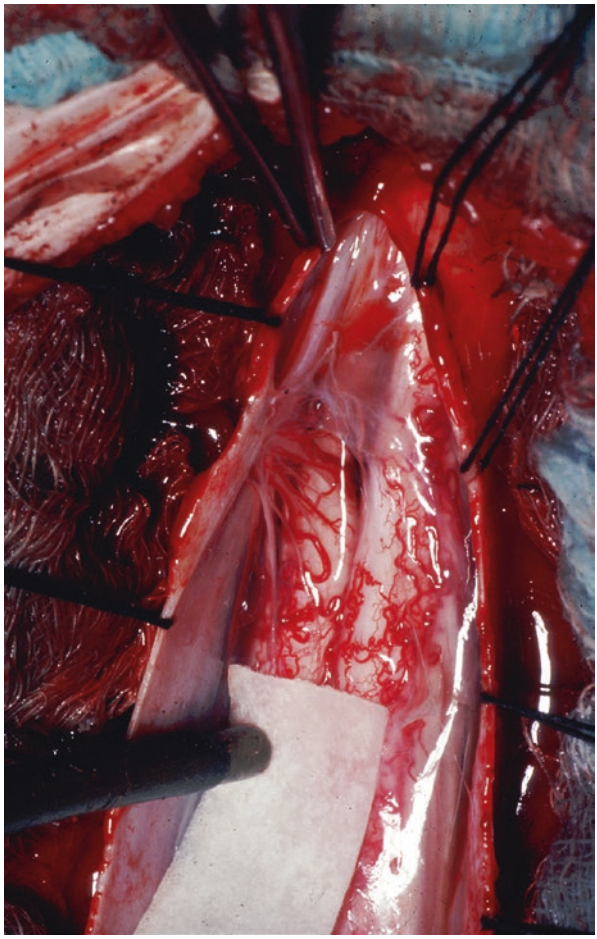

Fig. 13.2 Illustrated intraoperative view of one variety of meningocele manqué

All tethering tracts originate on the spinal cord, but discrepancies regarding their termination have also fueled challenges to MM. James and Lassman's original case series provided no strict limitations on MM tract termination, stating that intrathecal adhesions of MM are typically accompanied by extrathecal bands extending to the overlying neural arches, but subcutaneous attachments are uncommon [1]. However, their series harbors cases involving intradural, laminar, and cutaneous band termination (as accommodated by atretic meningoceles with direct connections to recurrent nerve roots and intradural adhesions), in addition to terminations within subcutaneous lipomas [1]. In 1977, James and Lassman provided a formal characterization of MM stating that bands can continue through the dura mater to terminate at the site of the defective lamina or carry on to a cutaneous termination, with or without cutaneous stigmata [2].

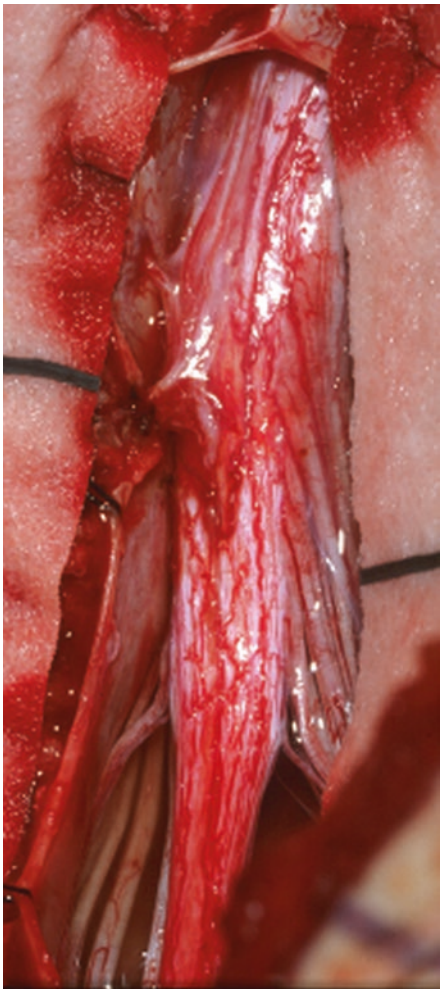

Fig. 13.3 Illustrated intraoperative view of one variety of meningocele manqué

As discussed further herein, the definition of MM as it pertains to tract termination has faced challenges, yet MM tracts can safely be defined as originating at the spinal cord and terminating in the dorsal dura, epidural space, or overlying lamina [3–7]. At surgery, Tubbs et al. found 63% of patients to have intradural bands extending between the spinal cord and inner aspect of the dorsal dura, while 37% had bands extending from the spinal cord through the dorsal dura mater and terminating on the underside of the lamina or within the surrounding fibrous tissue [5]. MM is typically located in the lumbar region of the spine but can occur in any region. Tubbs et al. found 42%, 26%, 11%, and 5.3% of bands in the lumbar, thoracolumbar junction, thoracic, and cervical spine, respectively [5]. The same series found 21%, 42%, and 21% of bands at levels 1, 2, and 3–5, respectively.

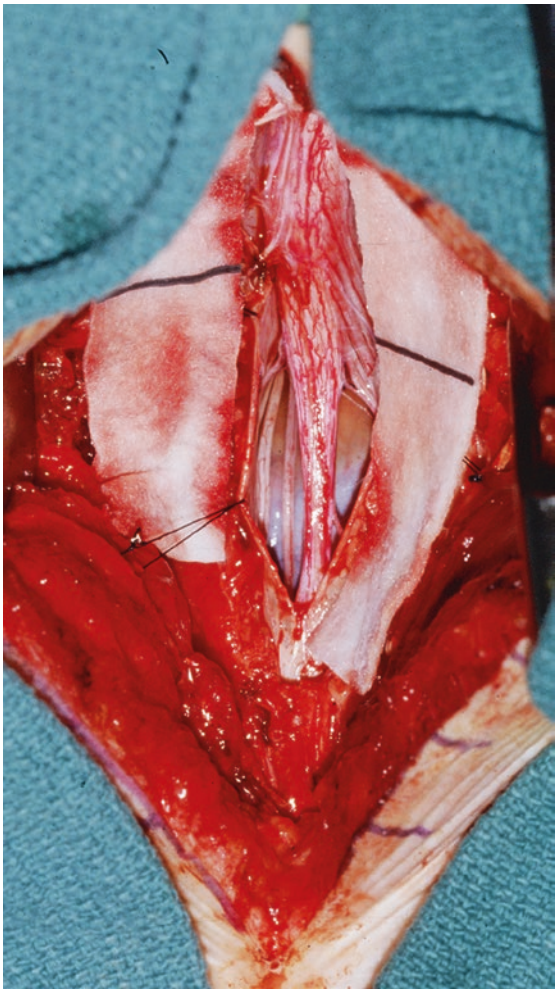

Fig. 13.4 Illustrated intraoperative view of one variety of meningocele manqué

Histological analysis has shown tethering bands to contain peripheral nerves, ganglion cells, adipose tissue, blood vessels (Fig. 13.3), epidermal cells, cartilage/bone, smooth muscle, CNS tissue, and dermal/epidermal cyst elements, in descending order of frequency [7]. Fibrous tissue is present in all tracts and is the most common constituent tissue, but a histopathological analysis of 20 tracts found no meningeal elements, contrary to the prediction of the abortive embryonic meningocele hypothesis [7]. This histological discrepancy came to serve as grounds for the first challenge to the term "MM."

An important set of variations comprises the ventral tethering bands associated with type II split cord malformation (SCM) [8]. Pang differentiates these ventral tethering bands from MM, stating six patients had MMs but none was on the ventral

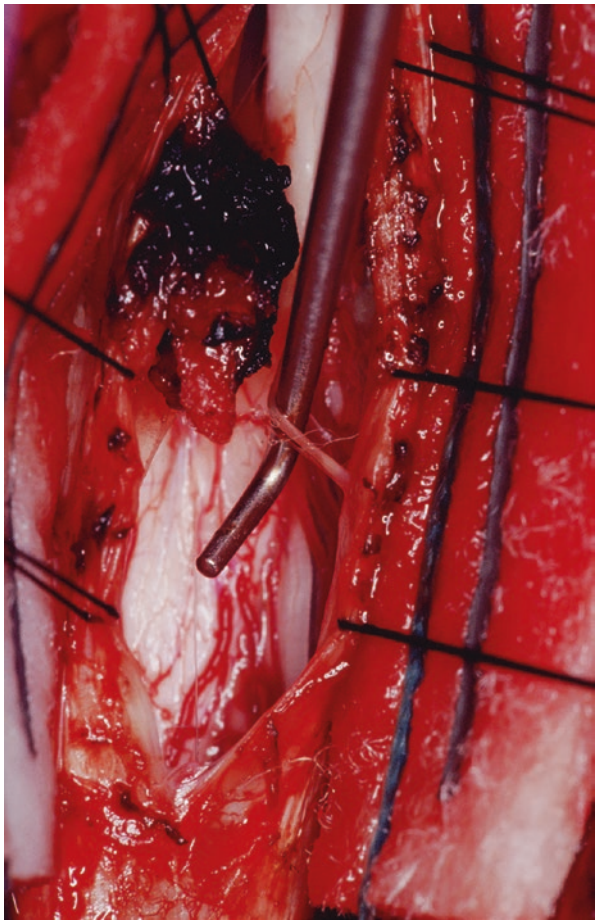

Fig. 13.5 Illustrated intraoperative view of one variety of meningocele manqué

side of the hemicord. Note that according to Pang, MM is defined by the paramedian dorsal nerve roots and ganglia cells lying alongside the fibrous bands, rather than the fibrous bands themselves [8].

Embryology

Spina bifida lies on the spectrum of embryological abnormalities arising from focal failures of midline fusion, which characterize spinal dysraphism. In spina bifida occulta, the anomalies are predominately confined to bony spinal elements, and all defects remain covered by a layer of skin, as opposed to the open defects of spina bifida cystica.

There are many hypotheses about the embryological origins of MM. The classic originally proposed by James and Lassman was that the bands arise from meningoceles that failed to form and atrophied during development [1]. While devoid of

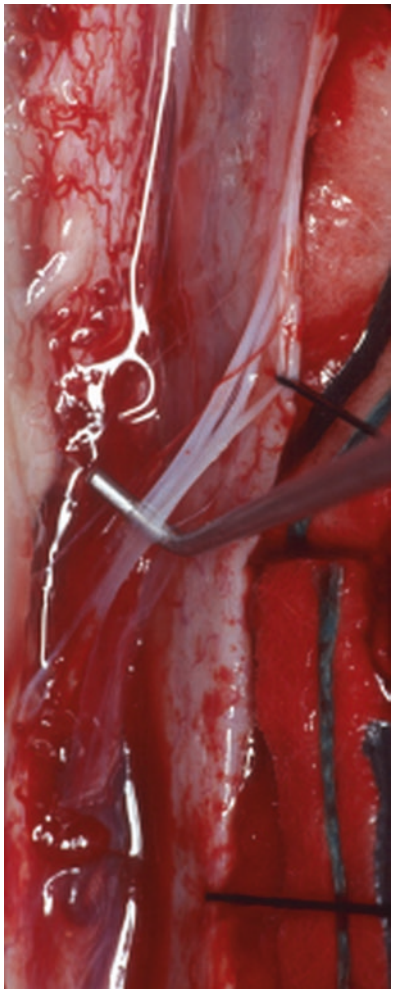

Fig. 13.6 Illustrated intraoperative view of one variety of meningocele manqué

functioning neural elements, recurrent nerve roots often attach themselves to the neck of the meningocele sac, causing neurological deficits both at birth and later in life [1]. James and Lassman believed nerve roots and fibrous bands adherent to the dura mater represented the site of herniation of the abortive meningocele, the extent of tethering depending upon the stage of development at which the meningocele formed and on how rapidly it was arrested.

An alternate hypothesis holds that tethering bands and adhesions are formed secondary to abnormal regression of the caudal neural tube [9]. Secondary neurulation gives rise to the caudal neural tube and results in the formation of the medullaris, cauda equina, and filum terminale from the caudal cell mass. Regression of the caudal neural tube follows secondary neurulation, beginning between days 43 and 48 of development [9, 10]. During this period, the ventriculus terminalis, along with the conus medullaris, undergoes a relative ascent within the spinal canal to

accommodate the disproportionately growing bony spinal elements. Abnormalities affecting this process have been attributed to band and adhesion formation in tethered cord syndrome and could account likewise for the similar structures of MM.

In their Unifying Theory of Embryogenesis, Dias and Walker propose that complex spinal dysraphisms arise from disordered gastrulation, in which the separation of notochordal precursor cells and paired prospective neuroepithelial cells flanking the primitive streak leads to the independent development of bilateral cell populations, resulting in a set of paired hemicords (on two hemineural plates) with primitive streak cells separating them [11]. The extent of the defect, as well as its repair, determines the extent of the subsequent dysraphism. The relevance of this perspective to MM lies in its claim that mesodermal differentiation of the pluripotent cells remaining after the dissolution of intervening primitive streak cells can result in the formation of fibrous bands, fibroadipose tissue, muscle, and aberrant blood vessels [11].

Pang's hypothesis of ventral tethering in split cord malformation (SCM) calls for an endomesenchymal tract, formed secondary to a failure of midline integration between prospective notochordal cells, that creates a midline area of persistent ectoderm and endoderm adhesion (and subsequent mesenchymal cell association) separating the two heminotochords [8, 12]. Similar to the Dias and Walker hypothesis, the final malformation depends on developmental factors following heminotocord formation. Specifically, the availability of primitive meninx cells is presumed to determine whether the hemicords will form independent dural sacs separated by a bony spur (type I SCM) or remain within a single dural sac, *sans* intervening spur (type II SCM) [8, 12]. In these cases, myelomeningocele manqué can be observed as fibrous bands (of putative mesenchymal origin) and paramedian dorsal nerve roots and ganglion cells (putatively arising from neural crest cells within the endomesenchymal tract) extending alongside one another, from the dorsal medial aspects of the hemicords to the dorsal dura mater [8, 12]. As previously stated, MM is characterized, in Pang's view, by the nerve roots and ganglia cells extending between the hemicord and dura mater, rather than by the associated fibrous bands. Under this definition, Pang states that MM can never occur ventrally, as neural crest cells (the cells giving rise to the nerve roots and ganglion cells of MM) are not located ventral to the neural plate [8].

Presentations

James and Lassman's original 45 MM patients presented with symptoms and abnormalities classically associated with dysraphic conditions, including physical malformations, urinary incontinence, abnormal reflexes, and spasticity [1, 2]. Tubbs et al. and Kaffenberger et al. have provided the two most comprehensive series of surgically proven MM patients [5, 13]. Between the two series, lower motor neuron disturbance was the most common presentation, followed by pain, upper motor neuron disturbance (hyperreflexia), bladder and bowel deficits, sensory deficits, pedal

deformities, and sexual impotence [5]. Note that the presenting neurological deficits in MM differ little from those found in other dysraphic anomalies [2, 13].

The mean age at presentation is around 11 years but ranges widely from 1 day to 38 years [5, 13]. Tubbs et al. reported that 72% of patients demonstrated abnormal neurological examinations at presentation [5]. Interestingly, Kaffenberger et al. indicated that within their series, progressive sensory and motor deficits typically presented in older patients, while the signs and symptoms of younger patients remained simply "suggestive" of an underlying pathology [13].

The degree of cutaneous evidence is presumably related to the developmental stage at which the defect originated [1]. James and Lassman originally described presentations including hypertrichosis and scarred or unscarred nevi, although 19 of their 45 cases (42%) presented with no cutaneous marker [1]. Fifty-seven percent of patients in the Kaffenberger et al. series and 68% of those in the Tubbs et al. series presented with cutaneous stigmata including lumbosacral hirsutism, hemangioma, and subcutaneous lipoma [5, 13]. More recently, a cutaneous midline lumbosacral "cigarette burn" stigma, described as a small scarified area of abnormal skin, was found in roughly 55% of MM cases [14].

Imaging

MM typically represents an incidental finding during exploration of the spinal cord in cases of spinal bifida occulta, with limited literature concerning its radiological presentation [2, 3, 8, 13, 15]. On myelography, James and Lassman found MM to be associated with a low lying conus medullaris (41% of cases), midline filling defects due to thick or clustered intradural bands (27%), thickened filum terminale (18%), and other abnormalities (11%), including an abnormal course of the cauda equina or conus medullaris [2].

Kaffenberger et al. retrospectively analyzed the CT and MR images of 16 patients with surgically proven MM [13]. MM was revealed in only four out of ten CT images with intradural water-soluble contrast, appearing as thin filling defects, extending between the origin at the spinal cord or hemicord to the dorsal dura [13]. In line with this, Pang reported that CT myelography predicted ventral tethering in roughly 50% of patients [8].

Because they are small and there is loss between imaging slices, the tracts of MM are not reliably appreciated via MRI (Fig. 13.4). Kaffenberger et al. reported that 55.5% of cases demonstrated findings suggestive of MM on T1-weighted axial MRI, with bands appearing as thin structures isointense to the spinal cord extending between it or a hemicord and the dorsal dura mater [13]. In total, 56% of patients with surgically proven MM revealed evidence of tethering bands on imaging [13]. That 40% of bands were unidentifiable via CT or MRI, despite retrospective knowledge of their presence, should indicate the ease with which these bands can be overlooked preoperatively and should lead the surgeon to maintain high intraoperative suspicion for such structures.

Associated Conditions

James and Lassman found MM to be primarily associated with SCM, lumbosacral lipomas, and atretic meningoceles [1, 2]. The association between MM and SCM is quite strong, underlying much of the surgical wisdom regarding exploration of SCM patients. Of their original 45 MM cases, 28 (62%) were associated with SCM: 18 (64%) type II and 10 (36%) type I [2]. Eighteen of 32 (54%) type II and 10 of 42 (24%) type I SCM cases were associated with MM [2]. Kaffenberger et al. reported an association between MM and SCM in 87.5% (43% type II, 57% type I), while Tubbs et al. found an association in 74% [5, 13]. In all cases, tethering bands typically originate at the dorsal medial aspect of the hemicord before coursing to the dorsal dura mater. In SCM cases, inclusions of the conus medullaris or hemicord are always present, and tracts most frequently terminate at the dorsal dura mater. However, as with other tethering bands of MM, these bands can terminate at the inner aspect of the dura mater or course further externally to terminate on to a lamina [7]. As previously discussed, tethering bands can also be found on the ventral aspects of SCM hemicords and are reported to occur in 21% of patients with a type II SCM [8].

James and Lassman reported that 17 of their 45 MM cases (38%) were associated with lumbosacral lipomas and SCM [2]. Subsequent reports have confirmed that MM occurs in conjunction with lumbosacral lipomas and SCM and have shown additional associations with syringohydromyelia and Klippel-Feil syndrome [3–5, 13, 16–19]. A study of 27 patients with terminal syringohydromyelia showed MM to be the second most commonly associated condition (54%) [19]. MM is more commonly associated with large syringes and is present in combination with SCM.

Kriss et al. published a case in which MM was associated with a true meningocele [3]. The conus medullaris was tethered dorsally by a band of aberrant nervous and fibrous tissues extending from the caudal spinal cord to a meningocele, causing dorsal displacement of the intradural elements [3]. This is self-evidently problematic as recurrent nerve roots are commonly found at the necks of meningoceles and do not represent cases of MM. Indeed, this feature of meningoceles inspired James and Lassman's use of the phrase "MM." However, in the paper, the progressively loose use of the term and previous association of MM with meningoceles was used to justify its application in this case [3].

James and Lassman stated that in their experience, when dermal sinuses were not associated with dermoid cysts, they were likely to contain intrathecal anomalies such as MM [2]. However, the nature and extent of the association remained unclear. MM tracts have since been described in association with dermoid cysts and dermal sinus tracts (DST) [5, 13], but the validity of any association between MM and DSTs has since come under scrutiny.

Alternative Classifications

It would seem to follow from the term MM that all bands/tracts falling under this designation are of meningeal origin and contain meningeal elements. While there is

mention of histopathological confirmation of these elements in bands in the original case series, most bands in MM predominately comprise fibrous tissue and often contain atretic nerve roots [1, 2, 7]. For this reason, James and Lassman believed that MM is better defined at operation rather than strictly through histology. It must be kept in mind that James and Lassman repeatedly acknowledged that the term "MM" was introduced as a matter of convenience to provide the authors with a better alternative to "dorsal tethering bands and adhesions" [1, 2].

However, confusion regarding the entity drove a histopathological investigation into the composition of tethering tracts, which called the use of the term "MM" into question [7]. Rajpal et al. were the first to confirm the cellular composition of tethering tracts. Fibrous connective tissue was the most common finding, followed by peripheral nerves, ganglion cells, adipose tissue, blood vessels, epidermal cells, cartilage/bone, smooth muscle, CNS tissue, and dermal/epidermal cyst elements [7]. However, using standard H&E staining and EMA immunolabeling (a marker demonstrated to show positivity for meningeal elements), none of the tracts tested contained meningeal elements. Given these results, Rajpal et al. deemed MM an inappropriate term [7].

They found that most tracts originate from the spinal cord [7]. Additional origins included dermoid cysts and lipomatous tissue. Tracts terminated at the skin, deep surface of the lamina, dura mater, and the extradural space between the dura mater and lamina [7, 13]. In light of these findings, Rajpal et al. proposed that tracts should be classified as short tethering tracts (STTs), terminating within the dura mater, epidural space, or lamina, or long tethering tracts (LTTs), terminating in the overlying skin. LTTs were further subdivided into epithelial LTTs, containing epithelial elements or associated with inclusion cysts, and non-epithelial LTTs, without epithelial elements or inclusion cyst associations [7]. On the basis of differences in histology and location, STTs and LTTs were believed to be attributable to distinct embryological errors, while epithelial and non-epithelial LTTs were posited to lie on an embryological spectrum, the two being distinguished by variations in timing [7].

The next set of classifications was proposed van Aalst et al. in 2009 [20]. These authors took the epithelial and non-epithelial LTTs of Rajpal et al. and renamed them congenital dermal sinus tracts (DST) and dermal-sinus-like stalk (DSLS). A squamous epithelium-lined tract with a hollow central lumen and an open skin defect characterized the DS. Such features make a DST prone to infection, a particularly dangerous feature when it terminates intradurally. In contrast, a DSLS is characterized by fibrous composition, lack of a central lumen, and a closed dimple. Histopathological analysis showed DSLS to comprise mesenchymal and neural elements. Given the lack of lumen and closed cutaneous defect, no DSLS patients presented with intraspinal infection [20].

Martinez-Lage et al. followed with a paper again reclassifying epithelial and non-epithelial LTTs as DSTs and *pseudo*-DSTs [21]. The fundamentals of their classification were essentially those of van Aalst et al. (i.e., DSLS equates to *pseudo*-DST). In the 20-patient series, 8 patients had proven DSTs, while 12 children had proven *pseudo*-DSTs [21]. Five of the eight patients with DSTs presented with superficial or deep infections with associated cutaneous stigmata including a

pinpoint-sized lumbosacral orifice associated with a flat hemangioma ($n = 5$), subcutaneous swelling ($n = 5$), or a separate coccygeal pit ($n = 3$). DSTs were surgically discovered to end at the dura mater, spinal cord, filum terminale, or cauda equina in two cases each. In contrast to DST patients, *pseudo*-DST patients presented because of cutaneous stigmata or neurological involvement rather than infection [21]. The cutaneous stigmata included a translucent skin-covered dimple (cigarette burn lesion or blister) in all cases, with an encircling flat hemangioma ($n = 4$) or an associated subcutaneous lipoma ($n = 7$) and hypertrichosis.

Non-epithelial LTTs, dermal-sinus-like stalks, or *pseudo*-dermal sinus tracts go by one other name in the literature, limited dorsal myeloschisis (LDM), under which the two largest case series for this anomaly are classed [6, 22–24]. Such variant terminologies have obviously resulted in confusion among similar reports in the literature [25, 26].

Treatment

Surgical treatment primarily involves freeing the tethering nerve roots and dorsal bands from their points of adhesion. When this proves impossible, tension is relieved by circumferential dissection of the area of dural attachment [1, 2]. James and Lassman noted that dissection of the filum terminale can also be required when this structure is part of the adhesion area. If there is doubt about the point of adhesion in the filum terminale, the authors recommended caudal division of the adhesion [1, 2]. Extradural bands extending into overlying laminae are commonly nonfunctional and can safely be removed [2]. Note that the dural attachment of extradural bands is almost invariably associated with intradural dorsal tethering bands. Care is therefore needed in removing the lamina to avoid inadvertent traction on underlying neural tissue.

Following surgical intervention, and a mean follow-up period of 11.5 years (range 3 months to 18 years), Tubbs et al. reported improvement of neurological symptoms over initial presentation in 37% of their patients; 47% had unchanged findings, and 16% showed deterioration of neurological symptoms [5].

The high comorbidity of MM with SCM emphasizes the need to examine for these bands during surgical exploration of SCM patients [1, 2, 8, 13]. Kaffenberger et al. advise that the likelihood of discovering functionally relevant medial bands, even in patients without a septum, is great enough to warrant surgical intervention [13].

Of patients with type II SCM, up to 21% harbor ventral tethering bands, roughly 40% of which were predicted to have remained undetected without surgical intervention [8]. In his analysis of ventral tethering, Pang found a sizable increase in neurological progression and a likelihood of myelopathic signs in patients with type II SCM who had ventral versus dorsal tethering bands [8]. These results highlight the need not only to explore all cases of SCM but also to examine both the dorsal and ventral aspects of the hemicords for tethering structures.

A final consideration is that tethering bands are often found distal to the site of any additional dysraphisms, meaning exposure of the entire dysraphic area is

necessary during surgery [5]. Failure to identify and untether dorsal bands intraoperatively can result in an unsuccessful detethering.

Conclusions

Per James and Lassman's original characterization, MM results from a minor defect late in embryonic life that arrests the organization of the meningocele into a complete structure. These failed structures revert into fibrous tissue and were presumed to absorb meningeal elements extending between the thecal sac and the overlying lamina or skin, forming adhesions involving various neural structures [1, 2]. From subsequent work characterizing DST and LDM, it is clear that the original definition of MM was too broad, inappropriately incorporating distinct embryological entities.

While a thorough analysis of this body of work is beyond the scope of our paper, there is an important inference for our characterization of MM. In each of the aforementioned papers examining STTs, DST/epithelial LTT, and non-epithelial LTT/*pseudo*-DSTs/DSLS/LDM, the authors mention that these anomalies were previously labeled "MM." Such classification errors have been evidenced throughout this paper and date to the original characterizations of MM by James and Lassman [1–3, 5, 8, 13]. Importantly, while certain distinct anomalies have been removed from under the umbrella of MM and reclassified into DST and LDM, there remains a group of tethering band anomalies for which there is still no better term than MM.

While this group could yet be further subdivided, MM can safely be characterized for now as tethering of the spinal cord, nerve roots, and/or filum terminale by single and/or multiple aberrant nerve roots, fibrous bands, and/or adhesions which terminate on to the dorsal dura mater, epidural space, or overlying lamina. MM shows a high association with SCM (particularly type II SCM), and in these cases, care must be taken to search for ventral as well as dorsal tethering bands.

Conflict of Interest The authors declare no conflicts of interest.

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Terminal Syringomyelia and Occult Spinal Dysraphism

14

Nidal B. Omar and James M. Johnston Jr.

Introduction

Terminal syrinx (TS) is traditionally defined as an intramedullary cystic dilatation of the caudal third of the spinal cord [1]. It is commonly associated with and occurs cephalad to diverse expressions of occult spinal dysraphism (OSD), including split cord malformation, lipomyelomeningocele, dermal sinus tract, fatty filum, anorectal anomaly, and meningocele manqué. The incidence of TS has been reported in 6–46% of cases of OSD evaluated by MRI (Table 14.1). Presenting symptoms are similar to OSD without TS and may include bowel or urinary bladder dysfunction, orthopedic deformity, back pain, and lower extremity motor and/or sensory deficits. As with the other OSDs, TS may be associated with cutaneous hemangiomas, hypertrichosis, and bony dysraphism. There is some controversy in the literature regarding the independent clinical significance of TS in the symptomatology of patients with OSD. Direct treatment of the syrinx by either myelotomy/aspiration or syringo-arachnoid shunt (SAS) in addition to untethering of the OSD has been advocated [1, 2] but is controversial; other authors have reported that treatment of the OSD alone results in similar rates of clinical improvement, without the morbidity of aspiration or shunting [3–6]. Similarly, there is not a consistently reported correlation between syrinx resolution and overall symptomatic improvement after cord detethering, with or without direct syrinx drainage or shunting [6].

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Table 14.1 Incidence of terminal syrinx associated with occult spinal dysraphism (OSD)

Study	Number with OSD	Associated terminal syrinx (%)
Schlesinger et al. (1986) [18]	13	46
Jaspan et al. (1988) [19]	37	40
Brophy et al. (1989) [20]	25	24
Raghavan et al. (1989) [21]	20	45
Scatliff et al. (1989) [22]	104	6
Taviere et al. (1989) [23]	16	25
Gupta et al. (1990) [24]	15	30
Bradford et al. (1991) [25]	42	10
Tripathi et al. (1992) [26]	95	26
Iskandar et al. (1994) [1]	90	27
Koyanagi et al. (1996) [4]	34	24
Erkan et al. (1999) [10]	132	24
Sade et al. (2003) [13]	62	37
Lee et al. (2012) [6]	135	24

Pathogenesis

The pathogenesis of terminal syringomyelia in OSD is thought to be quite distinct from that of syringomyelia associated with hindbrain anomalies and classic hydrodynamic theories of syrinx formation [1]. Given the spatial location of TS-associated syrinx just cephalad to the OSD, a cause-effect relationship has been postulated, with theories suggesting either embryological or local scarring mechanisms of syrinx formation.

TS has been theorized to represent a persistent ventriculus terminalis that fails to regress during secondary neurulation, resulting in a persistent ependymal lining after retrogressive differentiation, with subsequent cystic dilatation [2]. This concept has the limitation of not explaining the phenomenon, albeit rare, of terminal syringes that develop after initial detethering. Animal studies have suggested arachnoiditis and scarring may cause obstruction and backup of fluid in the central canal, leading to TS [7, 8]. Imaging findings of diminutive or obliterated subarachnoid spaces and increased local cerebrospinal fluid turbulence have been used to support this theory [2]. However, these findings are not typically seen at the time of initial detethering operations. Hall et al. suggest that ischemia in watershed regions may account for cystic or ex vacuo changes in the central canal cephalad to the OSD [9], possibly secondary to vascular insufficiency in the setting of cord stretch due to tethering [2, 10]. However, this theory does not sufficiently account for cases in which the terminal syrinx regresses after OSD repair and without direct drainage or shunting.

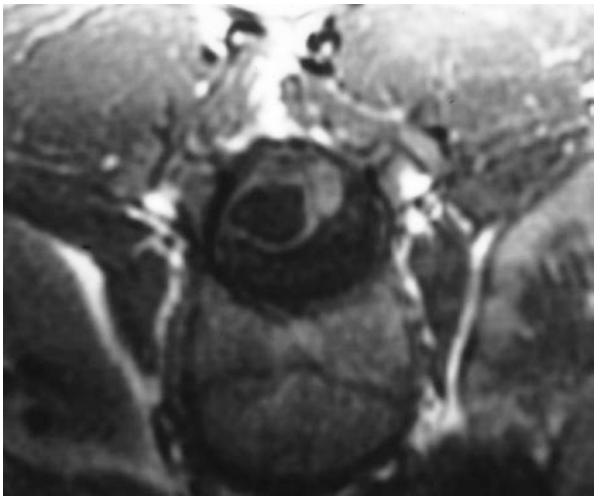

Fig. 14.1 Axial MR image with a large syrinx, expanding the distal cord + aspects of a split cord malformation. The syrinx is only present in one hemicord

Clinical Presentation

It can be difficult to distinguish symptoms attributable to TS from those related to an underlying OSD prior to treatment. In general, patients may present with pain, motor/sensory disturbances, foot deformity, spasticity, and bowel/bladder dysfunction as well as stigmata including cutaneous signatures or radiological evidence of dysraphism.

Imaging

Although sometimes apparent on ultrasonography in infants, magnetic resonance (MR) imaging is currently the gold standard for identifying and evaluating terminal TS. In addition to the invasiveness and added risk of arachnoiditis, CT myelography likely underestimates its incidence [1] and has fallen out of standard use since the advent of MR. Cystic dilatation in the lower one third of the spinal cord is the classical finding, with a wide range of diameters and appearance (Figs. 14.1, 14.2, and 14.3). Some authors have described a "syrinx index" in their inclusion criteria, quantifying the percentage of syrinx to spinal cord cross-sectional area in the region of largest syrinx diameter. One such study advocated a syrinx index of >40 as definitive of TS [6]. Other authors define "small syrinx" as one having a cord cross-sectional area of <50% and spanning a length of <2 cm, with a "large syrinx" as anything greater than 50% [1].

Occasionally, TS may be found as an isolated radiographic finding in a patient without other clear imaging findings but clinically suspected cord tethering. Careful review of the imaging is warranted to rule out other causes of syrinx, including Chiari malformation and OSD. Contrasted imaging is indicated, as rarely this may represent an atypical intramedullary tumor [11].

Fig. 14.2 Preoperative distal lipomyelomeningocele and a moderately sized terminal syrinx which expands the cord minimally

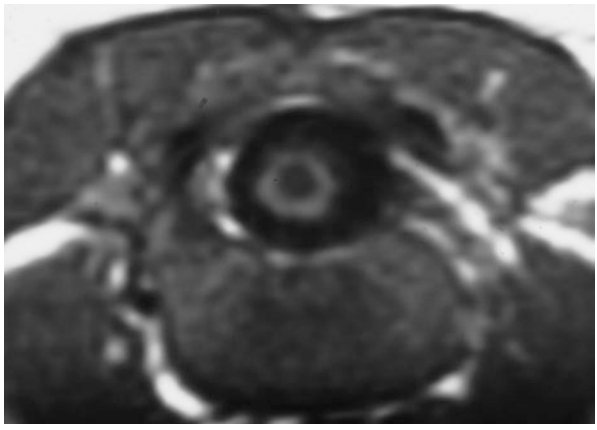

Fig. 14.3 Axial MR image of a typical small syrinx, unassociated with clinical symptoms

Management

The question of whether terminal syringomyelia constitutes a separate surgical entity from its commonly associated OSD remains controversial. Much of the existing literature details experience with treating syringomyelia in the setting of myelomeningocele, a clearly different entity than OSD. Except for rare cases of upper extremity weakness or clear dissociated sensory loss, it is almost impossible to differentiate symptoms attributable to TS as opposed to the OSD and spinal cord tethering. In addition, presenting symptoms typically improve following surgical management of OSD with cord detethering, and thus any indication of whether a terminal syrinx produces symptoms would be limited to experiences in patients with unrelieved symptoms after initial operative management who then had relief after subsequent, separate management of their syrinx.

Several series provide data suggesting that the majority of terminal syrinxes stabilize or regress after standard treatment of the underlying OSD (Fig. 14.4), without

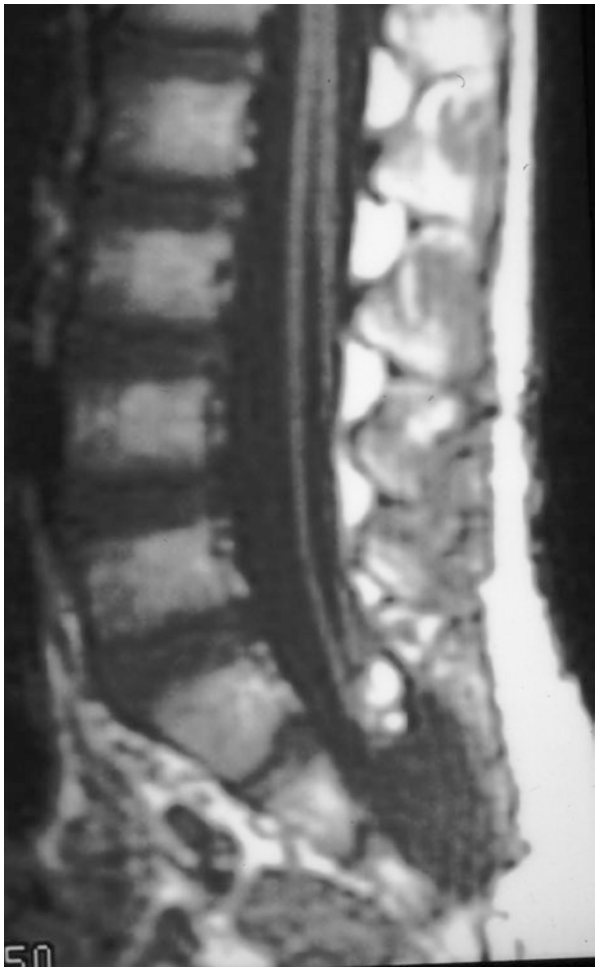

Fig. 14.4 Postoperative image of the same patient as Fig. 14.2 with persistence of the syrinx. With long-term follow-up (more than 10 years), the syrinx remained unchanged and the patient was without symptoms

the morbidity associated with direct aspiration or shunting of the syrinx [3–6, 12]. Lee et al. reported that 31 of 32 patients (97%) with OSD and TS showed long-term stability or decrease in the syrinx size following detethering only and a favorable clinical outcome in patients with unchanged syrinx size [6]. Kulkarni et al. posit a benign natural history for TS, with improvement in both the radiographic appearance of the syrinx as well as symptoms after treatment of the underlying OSD without direct syrinx intervention [12]. The authors point out that a dorsal myelotomy has the potential to cause permanent urinary bladder disturbance and must be weighed against a typically benign natural history. For the few patients that demonstrate expansion or develop worsening symptoms in a delayed fashion, retethering should be suspected. Transient enlargement of the syrinx in the postoperative period has also been described, but it should be noted that a syrinx stretched caudally under the tension of a tethered cord may recoil and appear larger in diameter once the tethered cord has been released [6].

Other authors have advocated a more aggressive approach to TS, with either myelotomy/aspiration or placement of a syringo-arachnoid shunt (SAS) [1, 2], especially in cases of TS with a large syrinx index (>50%). Iskandar et al. recommend direct treatment of large TS with myelotomy or SAS at the time of OSD repair/detethering. In this series, "large syrinxes" (as defined by cross-sectional area relative to the cord of >50% and spanning >2 cm in length) were considered symptomatic and treated with a midline myelotomy and SAS. Half of these patients were treated with only shunting, while the other half had their OSD concomitantly addressed. None of these patients worsened postoperatively, and the only patients that improved neurologically had undergone SAS. Based on these data, the authors advocate direct treatment of large terminal syrinxes to achieve better radiological and clinical results and to avoid future development of neurological dysfunction. Of note, the study was based on an older patient population (mean 14 years/median 12 years), presumably presenting later in their disease course, likely with larger TS and more severe deficits than seen in more recent pediatric series.

Similarly, Erkan et al. also recommend direct treatment of the terminal syrinx, in addition to standard detethering of the OSD. Most patients in this series were treated with a terminal syringostomy or simple midline myelotomy, with only one patient receiving a syringo-subarachnoid shunt [2, 10]. Outcome measures were sensory, motor, and bowel-bladder/sphincteric symptoms. None of the patients had craniocervical anomalies, hindbrain deformities, or hydrocephalus. The authors found that patients with a syrinx were more likely to have fecal incontinence and unilateral monoparesis preoperatively as compared to those without a syrinx. Outcomes were better in patients who underwent syrinx treatment, and they found this to be directly proportional to syrinx size on postoperative imaging, although this did not achieve statistical significance.

Rarely, progressive syrinx expansion with clinical deterioration after initial repair of OSD may require a second intervention, with some authors advocating simultaneous detethering with syrinx drainage [1, 4, 13] or syrinx drainage alone [14]. However, these conclusions are based on small series and it is not possible to make a definitive recommendation for best surgical treatment in this group.

In summary, given the wide range and limitations of data presented, most surgeons would advocate initial direct repair and untethering of the OSD, reserving syrinx aspiration or shunting for rare patients with large, progressive and clearly symptomatic TS that have not responded to initial and even secondary detethering procedures. Close follow-up of patients is mandatory.

Myelocystocele

Myelocystocele, constituting less than 5% of all cases of spinal dysraphism, is a disorder of secondary neurulation that may represent an extreme form of TS. Myelocystoceles may be continuous with TS and may also be associated with lipomatous mass. Typically, the low-lying spinal cord herniates dorsally through a bony defect before flaring into a CSF-filled, skin-covered "trumpet" that is continuous with the central canal [15–17]. Risk factors for development of myelocystocele include intrauterine exposure to teratogenic agents such as retinoic acid. In addition, there is a strong association with the OEIS syndrome (omphalocele, cloacal exstrophy, imperforate anus, spinal anomalies).

Essential and nonessential features have been proposed to define myelocystocele. Essential features include (1) an elongated cord that extends extraspinally into a cerebrospinal fluid-filled cyst that is broadly adherent to subcutaneous fat, and (2) functional conus that is confined to the proximal cyst/intraspinal cord, while the caudal cyst wall contains nonfunctional tissue. Fat, variable hydromyelia, and a caudal meningocele are considered nonessential features [16].

Histologically, the cystic cavity is lined with sparse ependymal cells and clusters of glial tissue surrounded by dense fibrous stroma and thick-walled blood vessels. Neural elements, including myelinated and unmyelinated nerves, irregular dorsal root ganglion cells, and entrapped neural crest progenitor cells, are present but irregular, without clear organization or structure. The conus medullaris and all functional sacral nerve roots either remain within the spinal canal or originate just outside of it before returning back into the canal and exiting out the appropriate neural foramina. Most of the dorsal cystic component of the myelocystocele is nonfunctional, made up of disorganized glioneuronal and ependymal elements that are inert to direct electric stimulation [16]. Embryologically, the myelocystocele resembles a transitory stage of late secondary neurulation in chicks in which the CSF-filled bleb-like distal neural tube bulges dorsally to fuse with the surface ectoderm before focal apoptosis detaches it from the surface. Pang et al. theorize that myelocystocele may be an abnormal preservation of the embryonic state, with a time-specific arrest of apoptosis that occurs just before dehiscence of the cystic distal cord from the future epidermis [16].

A detailed understanding of the pathoanatomy of myelocystocele dictates appropriate surgical management. Given the risk of neurological deterioration due to tethering and progressive injury to the conus, it is generally recommended to pursue surgical repair and detethering in a timely manner. Surgical repair typically involves a midline skin incision that incorporates the subcutaneous mass in addition to at

least one lamina rostral to the lesion. A wide laminectomy is performed for exposure of normal dura before it sweeps into the dorsal trumpet. The dura mater is opened rostral to the backward turn of the trumpet and caudally where the dura blends into subcutaneous fat. Identification and preservation of the proximal nerve roots and conus within or near the spinal canal is paramount. The functional conus is obliquely disconnected from the nonfunctional trumpet and subcutaneous fat and then closed to achieve a pial-covered stump. Use of a dural graft to ensure a capacious and watertight closure [16] and instillation of intrathecal hydrocortisone [15] may be used to minimize postoperative scarring and retethering. Outcomes after surgery are typically good, with almost all patients' neurological deficits either stable or improved following surgery. Similar to other skin-covered spinal dysraphisms, concomitant hydrocephalus requiring shunt placement is rare following repair.

Conclusion

TS refers to a cystic dilatation in the caudal third of the spinal cord and is commonly associated with occult spinal dysraphism (OSD). While the underlying pathophysiologic mechanism is not fully understood, it is most likely related to the OSD and embryological and ischemic/metabolic theories exist regarding its development. The independent clinical significance of OSD-associated terminal syringomyelia and the role for direct surgical treatment of the syrinx beyond standard detethering of the OSD remain controversial. Terminal myelocystocele may represent an extreme form of TS and should be repaired in a timely manner to avoid neurological deterioration due to cord tethering.

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Imaging of Occult Spinal Dysraphism

15

Krista Greenan, David Mirsky, and Todd C. Hankinson

Introduction

Over the last 30 years, neuroimaging has become substantially more sophisticated, and access to advanced imaging techniques has become more ubiquitous. This has dramatically improved the assessment of OSD. Clinical providers are more apt to order advanced imaging studies, such as fetal magnetic resonance imaging (MRI) for concerning prenatal ultrasounds and spinal ultrasounds or MRI spine studies in neonates with sacral dimples. Meanwhile, clinical research is catching up with clinical practice to determine the utility and significance of such studies.

Prenatal diagnosis of OSD is increasingly common, and advanced imaging techniques such as fetal MRI play an increasingly important role in counseling. Typically, OSDs are diagnosed prenatally when an open myelomeningocele is suspected on prenatal ultrasound and fetal MRI instead reveals a closed lesion. The roles of prenatal ultrasound and fetal MRI in the diagnosis and management of OSDs are still evolving.

Postnatal diagnosis of OSD includes the neonatal period and also the rest of an individual's life span. In cases of OSD with no clear cutaneous markers, imaging may not occur until much later in life, and controversy still exists about normal variants versus pathologic findings on MRI, particularly in the setting of possible tethered cord syndrome (TCS).

X-rays of the spine have minimal utility in the work-up of symptoms that may be attributed to OSDs, but X-rays obtained for other reasons may occasionally reveal incidental OSDs. While nonspecific, the "winking owl sign" on spinal X-ray represents an absent or distorted pedicle and can be indicative of OSD, warranting further investigation with more advanced imaging techniques. Computed

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tomography (CT) is useful in patients with complex bony deformity associated with OSD and can help with surgical planning, but is not the diagnostic standard for imaging of the neural elements in the evaluation of spinal cord tethering.

Currently, the definitive imaging modality for congenital spinal cord anomalies, including OSDs, is MRI. Sagittal and axial T1- and T2-weighted turbo spin-echo sequences without fat saturation are the most commonly employed. The addition of fat saturation sequences can sometimes be helpful, such as in cases of spinal lipoma and neuroectodermal cysts. Sagittal T1- or T2-weighted series are used to identify the level of the conus medullaris, and axial T1-weighted images can clearly identify fat within the filum terminale. Heavily T2-weighted images, such as constructive interference in steady state (CISS) and fast imaging employing steady-state acquisition (FIESTA), can help characterize fine structures, such as dermal sinus tracts or dorsal bands in meningocele manqué, and recently have been used to define neural structures preoperatively in lipomyelomeningocele [1]. Cine MRI studies and dynamic supine/prone MRI studies have been suggested to assist with identifying a tethered spinal cord, but this has had mixed results in the literature [2]. Advanced techniques such as spinal diffusion tensor imaging (DTI) and spinal diffusion-weighted imaging (DWI) are in their infancy but, in the future, may provide useful information about functional neural tissue in OSDs.

In this chapter, we describe the typical imaging findings for the most common OSDs, as well as address some of the controversies and diagnostic dilemmas that can arise when imaging this group of complex disorders. In the first section, which discusses imaging in cases with a clinical suspicion of tethered cord syndrome (TCS), the topics of nondiagnostic imaging in TCS, incidental fatty fila, and evaluation of the sacral dimple are discussed. The next section, on dermal sinus tracts, includes a discussion about related diagnoses, including the newer diagnostic entity of limited dorsal myeloschisis (LDM) and the more historical meningocele manqué. A third section discusses the imaging characteristics of lipomyelomeningocele, with a subsection on related diagnoses such as meningocele and myelocele. After discussions about neurenteric cysts (NECs) and split cord malformations (SCMs), we discuss future directions for imaging in OSDs.

Tethered Spinal Cord Syndrome

Tethered spinal cord syndrome is a variably defined clinical diagnosis that can include symptoms of low back pain, urinary incontinence or retention, severe constipation, and/or weakness or paresthesias in the lower extremities. Physical exam findings include lower extremity asymmetry, weakness on manual muscle testing, muscle wasting, paresthesias, in-turning of the foot, asymmetric plantar arches, or other subtle neuromuscular findings. Urodynamic testing can be positive for a neurogenic bladder. Electrophysiological testing can show increases in latency, decreased motor action potentials, and somatosensory evoked potentials [3].

Tethered cord syndrome can result from any pathological entity that places traction on the spinal cord, including such disparate diagnoses such as tumors, arachnoiditis, or congenital anomalies. Consequently, imaging characteristics of tethered

cord syndrome vary based on the underlying etiology. However, this syndrome is traditionally thought of as being secondary to a lesion exerting caudal traction on the spinal cord and is discussed in the context of the imaging findings of fatty filum terminale, thickened filum terminale, and low conus medullaris.

In cases of fatty filum terminale, a fat signal within the filum terminale is seen. This can be seen on spinal ultrasounds on neonates, but is most easily appreciated on axial T1-weighted imaging, and sometimes visible as a T1 hyperintense linear streak within the filum on sagittal views (Fig. 15.1). A thickened filum is defined as a filum greater than 2 mm in thickness [4, 5]. This finding can be seen in isolation or in conjunction with other pathologies. Importantly, the diagnosis of a simple tethered spinal cord typically hinges on the presence of a low-lying conus medullaris, which may not be identified in conjunction with a thickened or fat-infiltrated filum.

A low conus medullaris is typically diagnosed when the tip of the conus is below the middle of the L2–L3 intervertebral disc space. The conus is easily identified on sagittal T2-weighted imaging, but the level should be correlated with images

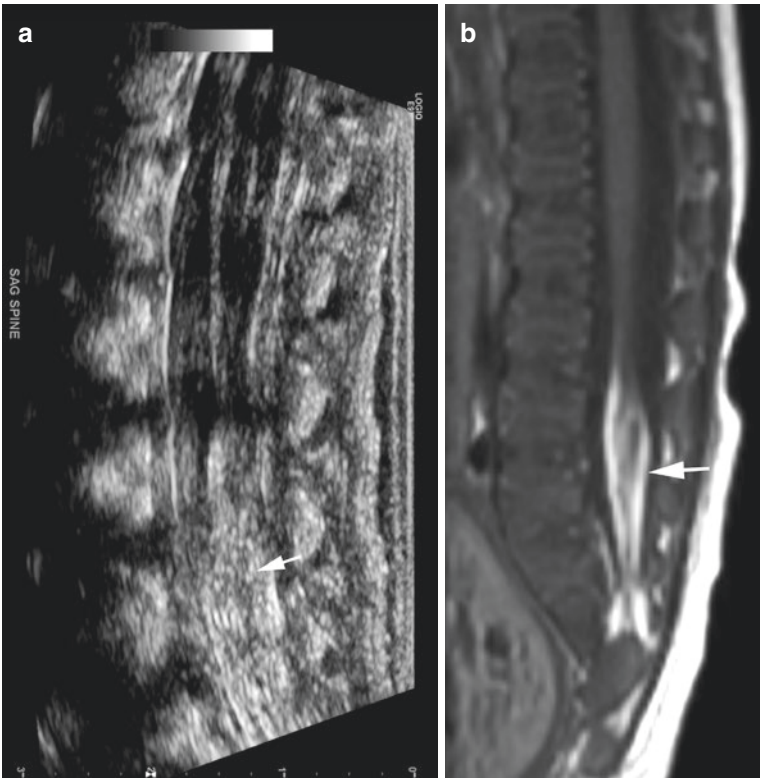

Fig. 15.1 (**a**) Sagittal grayscale sonographic image demonstrates a hyperechoic intradural mass (white arrow) within the distal aspect of the spinal canal. (**b**) Sagittal T1-weighted MR image more completely defines the presence of a lipoma (white arrow) tethering the spinal cord

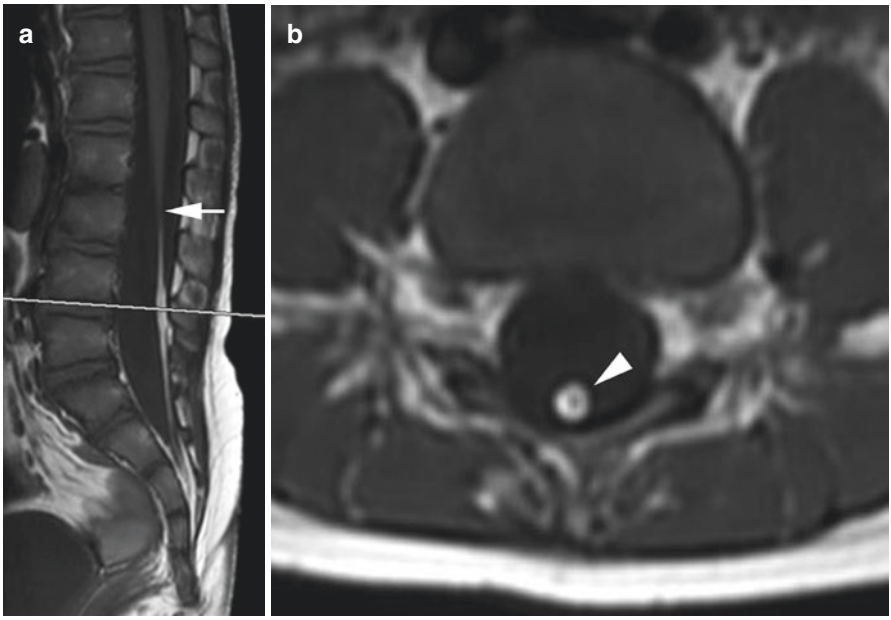

Fig. 15.2 (**a**) Sagittal T1-weighted MR image reveals a low-lying conus medullaris (white arrow), secondary to a linear streak of fat infiltrating the filum terminale. (**b**) Axial T1-weighted MR image (at the level of the reference line in Figure **a**), illustrates the cross-sectional circumference of the filum lipoma (white arrow)

acquired in the axial plan (Fig. 15.2). During fetal development, the spinal cord ascends within the spinal canal, as the growth of the spinal column is more rapid than that of the spinal cord itself. Using ultrasound, Perlitz et al. determined that the level of the conus can be determined at 20–24 weeks' gestation in about 70% of fetuses. By 24 weeks' gestation, 93% of the scanned fetuses had a conus ending height adjacent to the L2 vertebral body [6]. In full-term infants, Sahin et al. reported that the normal level of the conus medullaris is typically above L2 [7].

Another radiographic finding that is less common but may be associated with tethered cord syndrome is terminal syringohydromyelia [8, 9]. Terminal syringohydromyelia is a cystic dilation of the lower third of the spinal cord, starting immediately superior to the filum terminale and tracking cranially. Lack of contrast enhancement distinguishes it from other lesions of the conus medullaris.

However, this finding can be confused or conflated with a mildly dilated distal central canal, sometimes referred to as a terminal syrinx, terminal ventricle, fifth ventricle, or ventriculus terminalis [10] (Fig. 15.3). A ventriculus terminalis is a small, ependyma-lined, oval, cystic structure positioned at the transition from the tip of the conus medullaris to the origin of the filum terminale. This develops during embryogenesis as a result of canalization of the spinal cord and can be sometimes seen in newborns on spinal ultrasound [11]. It typically regresses in size during the 1st weeks after birth but has been reported in children up to 5 years old as a normal finding [12]. On MRI, the ventriculus terminalis is a non-enhancing,

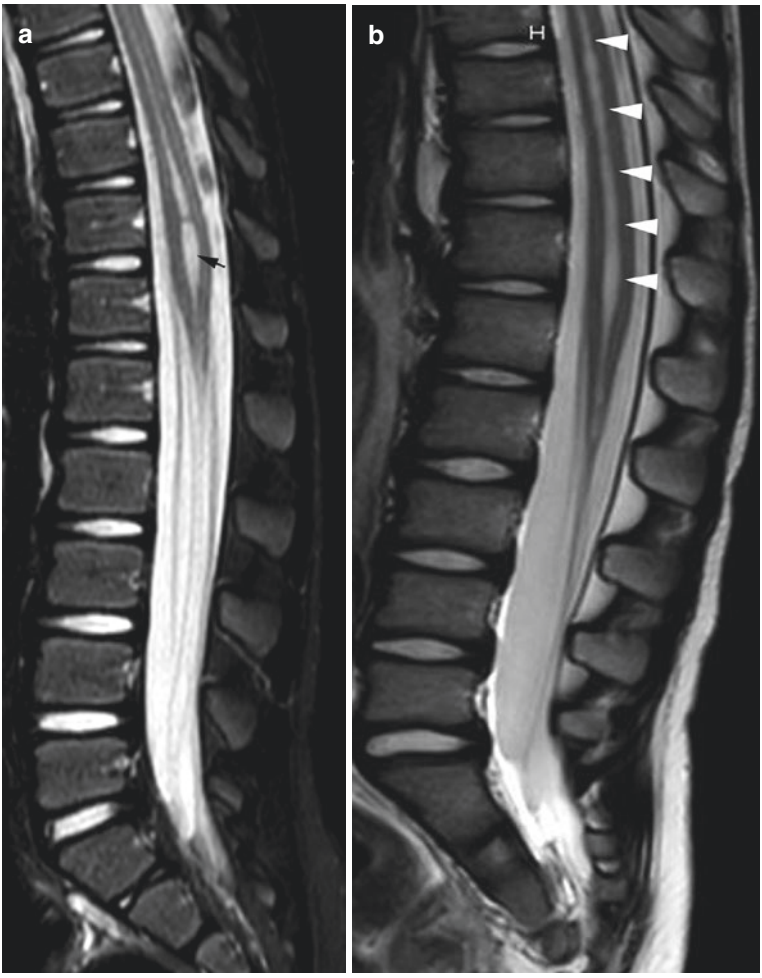

Fig. 15.3 (**a**) Sagittal T2-weighted MR image demonstrates mild cystic dilatation of the distal spinal cord, consistent with ventriculus terminalis (black arrow). (**b**) Sagittal T2-weighted MR image, in a different patient, shows cystic expansion of the distal spinal cord that extends above the level of the conus medullaris (white arrowheads), consistent with hydromyelia

ovoid, non-septated cystic structure localized to a normally positioned conus. One can distinguish a ventriculus terminalis from terminal syringohydromyelia by considering the size, morphology, and location of the dilation, as well as the age of the patient, and other concomitant lesions. Some authors posit that a dilated ventriculus terminalis can represent a pathological finding in older individuals, if associated with other lesions that are causing pressure or tethering on the spinal cord [12]. A single institution retrospective review of all pediatric patients with spinal MRI from 2002 to 2012 showed that there was no concordance between radiological terminal syrinx size and clinical deterioration, in both patients with and without scoliosis [13].

Tethered Cord Syndrome and Nondiagnostic Imaging

Classically, tethered cord syndrome is associated with the presence of a low-lying conus medullaris with or without a fat-infiltrated or thickened (>2 mm) filum terminale. There are reports suggesting that a patient who presents with clinical findings consistent with tethered cord syndrome, but with a conus at a normal level and no other radiographic findings, may still benefit from surgical untethering. Warder et al. first proposed that tethered cord syndrome can be seen in patients with a normal level conus with a series of 13 patients [14]. Fabiano et al. also presented a retrospective review of 22 cases of surgical untethering with nondiagnostic MRI findings: 73% of patients experienced subjective and/or objective improvement following surgical untethering [15]. A pathological analysis of sectioned fila showed more connective tissue with dense collagen fiber; some hyalinization and dilated capillaries were noted in patients with clinical tethered cord syndrome but normal imaging [16]. Another study by the same group showed that urodynamic studies were more important than radiographic findings in predicting which patients would improve from sectioning of the filum terminale. In patients who present with urinary incontinence, urodiagnostic studies that show hyperreflexic neurogenic bladder predicted improvement in continence with untethering, regardless of imaging findings. This included a subset of patients with normal imaging [17]. Lastly, Bao et al. presented a series of 60 pediatric patients with tethered cord syndrome but a normally positioned conus: all patients got better with surgery [18]. The authors concluded that pediatric tight filum terminale syndrome may involve a normally positioned conus.

Previously, prone imaging had been suggested to overcome nondiagnostic studies. Nakanishi et al. reported on 14 patients with occult tethered cord syndrome and found that, with MRI obtained in the prone position, the terminal filum was separated from the cauda equina and would also be shifted caudally to posterior in the subarachnoid space, with the cauda equina located anteriorly [2]. However, the validity of this imaging technique is not widely accepted or used in a clinical setting. One of the largest investigations of this imaging technique was a retrospective review of 51 patients who underwent supine and prone examinations. While the control group reliably exhibited consistent anterior migration of the conus within the dural sac, in the group of patients with OSD, postoperative imaging showed resolution of tethering on MRI in only 24% of patients, and the authors concluded that prone imaging is of no additional use in evaluation of spinal cord tethering [19].

Incidental Fatty Fila

With the overall increase in the use of axial imaging modalities, there is a growing body of literature documenting incidental radiographic findings, including those associated with tethered cord syndrome. Since 1994, when Brown et al. asserted that in the absence of symptoms of tethered cord syndrome, a fatty filum can be considered a normal variant, there has been confusion about what to do with an

incidentally discovered fatty filum [20]. A more recent study of adult patients receiving MRI L spine for various indications found that 37 patients (3.2%) were found to have fatty fila, and the group concluded that fatty fila likely represents an incidental finding in adult patients on routine lumbosacral MRI [21]. Al-Habib et al. looked at predictors of neurological compromise in adults with fat-infiltrated filum terminale. Through their retrospective chart review of 3853 adult MRI L spine imaging studies, they found only 9 patients with an isolated fatty lipoma: of those nine patients, the seven patients with a normal cord level were asymptomatic [22].

The implication of this group of publications is that infants who receive imaging for subtle cutaneous findings may be diagnosed with fatty fila of no clinical significance. It remains unclear if subtle radiographic findings alone merit surgical intervention in infants who are too young to have developed subtle neurologic symptoms associated with tethered spinal cord syndrome.

Radiographic Evaluation of the Newborn with a Sacral Dimple (and Other Simple Lumbosacral Cutaneous Findings)

In general, simple cutaneous lumbosacral markings, such as a simple sacral dimple or Y-shaped gluteal cleft, are unlikely to be associated with an underlying OSD. Nevertheless, in some practices, imaging is routinely obtained on neonates with simple sacral dimples and/or deviated gluteal clefts with the indication of "rule out tethered cord."

Much work has been done to evaluate the efficacy of spinal ultrasound in neonates with lumbosacral cutaneous findings. Several large ultrasound studies have shown that the risk of significant spinal malformations in neonates with isolated sacral dimples or gluteal clefts, who are otherwise healthy and asymptomatic, is exceedingly low [23–26]. Importantly, when the spinal ultrasound is obtained for multiple cutaneous stigmata, infants are up to six times more likely to have dysraphism diagnosed than those imaged based on a single marker [27].

Researchers have also looked at the necessity of using MRI in neonates and have found that the technique is more sensitive, with a positive finding ranging from 16.7% to 23%, with most of these patients diagnosed with a filar abnormality (fatty filum and/or low conus medullaris) [28–31]. However, the utility of such studies in asymptomatic infants, and what interventions should be performed, remain unclear.

Dermal Sinus Tract

A dermal sinus tract (DST) is an epithelium-lined tract that extends from the skin surface internally. These lesions are neurosurgically relevant because they sometimes reach the spinal cord, cauda equina, or arachnoid. DSTs are caused by incomplete fetal separation of the superficial ectoderm from the neural ectoderm, resulting in a focal segmentation adhesion. This manifests clinically as a small pinhole or dimple that is typically paramedian and is sometimes associated with hyperpigmented skin.

Additionally, soft tissue asymmetry and bony abnormalities are commonly associated with these lesions. While they can be found at any level of the neuraxis, DSTs occur most commonly in lumbosacral region and are often associated with a spinal epidermoid or dermoid cyst at the level of the conus medullaris or cauda equina.

Ultrasound, which is frequently used in neonates with lumbosacral cutaneous abnormalities, can show the entire length of the dermal sinus tract [11]. Although it is sometimes difficult to identify the lesion in the subcutaneous fat, tracts within the subarachnoid space can typically be demonstrated as hyperechoic.

As the current gold standard, MRI provides a more detailed anatomic description of the tract and its association with normal neurological structures or dermoid/epidermoid lesions. Frequently, tenting of the dural sac can be identified at the site of contact with the dermal sinus tract (Fig. 15.4). Local inflammation related to the sinus tract can lead to local enhancement on a post-contrast T1-weighted MRI. In a series by Barkovich et al., the subcutaneous portions of the spinal tracts and intramedullary portions of the congenital lesions were easily identified with the use of standard spin-echo techniques. However, except for limited areas where they were lined by fat, the intraspinal (extradural canal, epidural, subdural, and subarachnoid) portions of the dermal sinuses were poorly seen [32].

Limited Dorsal Myeloschisis

Limited dorsal myeloschisis (LDM) is a diagnostic entity introduced by Pang et al. in 1993 and clearly delineated in a 2010 case series of 51 patients [33, 34]. In this series, the authors defined LDM as "a distinctive form of spinal dysraphism characterized by 2 constant features: a focal 'closed' midline defect and a fibroneural stalk that links the skin lesion to the underlying cord" [34]. This entity is distinct from a dermal sinus tract, in that a dermal sinus tract is lined with epithelium and can be simplistically thought of as going from "out to in," whereas diagnostic criteria for an LDM require neural tissue within the fibroneural stalk and some relationship to the dura and underlying neural tissue, going "in to out."

Embryologically, LDMs likely result from incomplete disjunction and can include all manner of neural and nonneural tissues. Alternatively, DSTs are thought of as decedents of cutaneous endoderm. Technically, this would qualify LDMs as an "open" defect, and the term myeloschisis implies the open nature of the lesion, but given that the underlying spinal defect is frequently covered by skin, some have suggested the term "Transitional Spinal Dysraphism," and it is frequently discussed in the context of OSDs [35]. Undoubtedly, to date, diagnostic confusion has conflated the literature on the two entities.

The cutaneous findings related to LDMs can be variable. In comparison to dermal sinus tracts, which have pinhole or flat cutaneous findings, LDMs can be associated with findings ranging from normal spinal surface anatomy to large saccular lesions covered with thinned epithelium.

On imaging, the most clearly identifiable marker of an LDM is the stalk arising from the dorsal spinal cord and exiting the spinal canal (Fig. 15.5). As with DSTs,

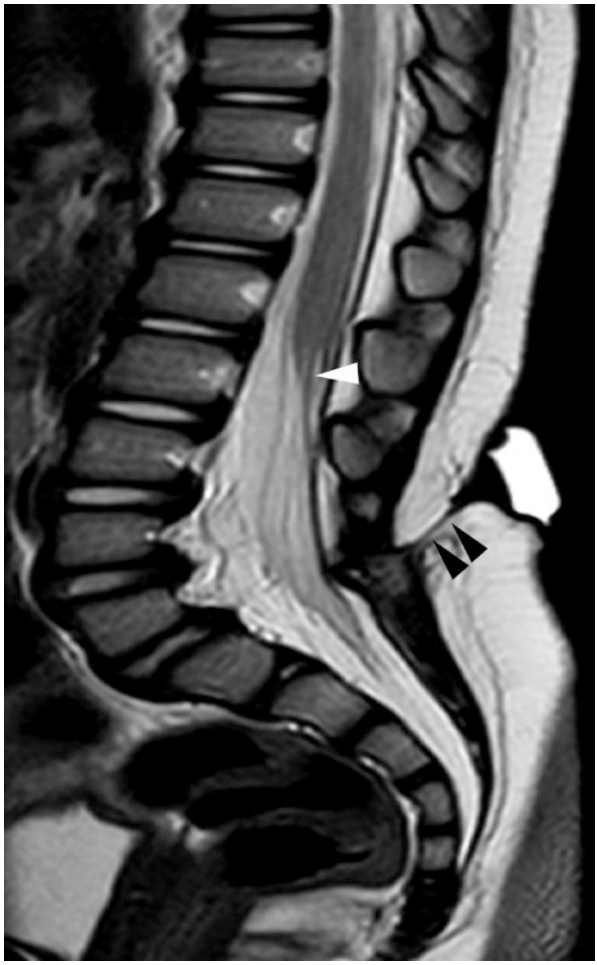

Fig. 15.4 Sagittal T2-weighted MR image demonstrates a hypointense dorsal dermal sinus tract within the subcutaneous tissues (black arrowheads). It enters the dural sac at L4–L5 and courses cranially, terminating at the conus medullaris (white arrowhead)

the level of the lesion is defined by where it exits the spinal canal, and tenting of the dura and spinal cord within the canal as the tract exits can frequently be seen. In a retrospective study that compared imaging characteristics of DSTs and LDMs, Lee et al. found significantly higher visibility of the intrathecal tract in LDM [36]. Additionally, the tract in LDM always can be seen attached to the spinal cord, whereas in DST, the attachment point is variable. Dorsal tenting of the spinal cord (as opposed to just tenting of the dura) is an imaging hallmark of LDM. A further distinction between DST and LDM is that the latter are generally not associated with infection or dermoid/epidermoid masses [36]. However, Eibach et al. reported 5 out of 75 cases of LMD that were with associated dermoid elements [37].

In addition to being discussed within the neurosurgery literature, LDM has been discussed extensively within the prenatal neuroimaging literature as a pitfall to be avoided when diagnosing open MMC in utero. Friszer et al. reported that out of 29 patients referred to a tertiary center for evaluation for fetal MMC repair, 6 cases

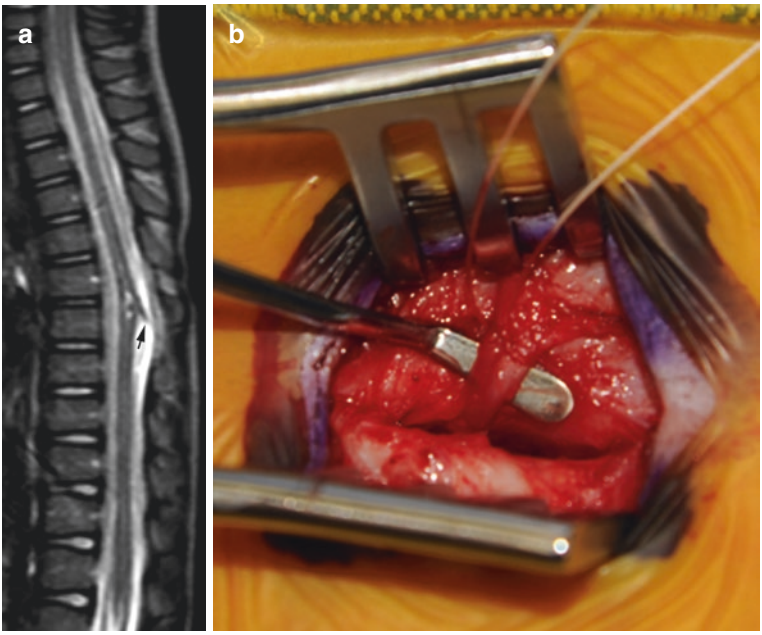

Fig. 15.5 (**a**) Sagittal T2-weighted MR image reveals a limited dorsal myeloschisis of the mid-thoracic spine, with dorsal tenting of the spinal cord at the site of attachment of the tract (black arrow). (**b**) Intraoperative image shows the tract where it enters the spinal canal

(20.6%) were re-diagnosed as LDM, characterized by a spinal saccular lesion with a thick peripheral lining in continuity with the adjacent skin. Within the saccular lesion, a thick hyperechoic well-delineated structure was present in continuity with the spinal cord [38]. Russell et al. presented a case of a very large thoracic lesion that was diagnosed on second trimester ultrasound as an open thoracic myelomeningocele with associated Chiari 2 malformation and moderate ventriculomegaly [39]. However, fetal MRI at 35 weeks proved the absence of a spinal defect. Upon birth, clinical examination and postnatal MRI confirmed the diagnosis of LDM. This child had an excellent neurologic outcome with no appreciable deficits after resection of the LDM. The take-away message from these reports is that in utero diagnosis of open MMC should be treated very cautiously and discussions with parents should take into account the fact that other diagnoses, such as LDM, can sometimes be mistaken for open MMC in utero.

Meningocele Manqué

Meningocele manqué (MM) has been historically conceptualized as "a meningocele that failed to develop." These lesions are described as dorsal tethering bands from the spinal dura to the surrounding tissues. They represent a form of OSD and can be identified on sagittal T1-weighted MR imaging as multiple small bands [40]. In a

2003 series of 19 patients, Tubbs et al. reported a high incidence of association with other forms of spinal dysraphism [41]. Pathologically, these lesions were defined as lined by meningeal tissue, as opposed to other types of dorsal bands that were made up of fibrous, neural, or vascular elements. However, in a histopathological review of dorsal tracts published in 2007, Rajpal et al. sought to clarify the various types of dorsal tethering tracts, and, with modern histopathological stains, no lesions met the pathological criteria for the diagnosis of MM [42]. The authors suggested that this diagnosis be retired and proposed an alternative classification system.

The classification and etymology of congenital spinal defects, both open and closed, has always been complex and fraught with inconsistencies. DSTs, LMDs, and MM are clear examples of this and, as more is learned about the embryology of these lesions, perhaps a more consistent approach can be adopted.

Lipomyelomeningocele

Lipomyelomeningocele is a congenital malformation characterized by the intimate association of neural and lipomatous elements in the context of midline mesodermal defects. These lesions are believed to result from failures of primary neurulation, in which mesenchymal tissue is intimately associated with the neural placode and forms lipomatous tissue. Lipomyelomeningoceles are always associated with a spinal bifida but can exhibit a great deal of variability from patient to patient and can also be associated with segmentation anomalies and concomitant dysraphic anomalies.

Lipomyelomeningoceles are typically diagnosed at, or soon after, birth based on clinical appearance. However, reports of diagnosis on fetal imaging are becoming more common. Felekis et al. reported a diagnosis of lipomyelomeningocele that was made on prenatal ultrasound and confirmed on fetal MRI [43]. At 22 weeks' gestation, the prenatal ultrasound showed an echoic semisolid subcutaneous mass covered by skin, posterior to the lumbosacral spinal canal of the fetus.

After birth, lipomyelomeningoceles have a distinctive appearance on physical exam, characterized by a large fatty mass in the lumbosacral region, covered with full thickness skin and deviating the gluteal cleft. The natural history of these lesions is not well characterized, but patients who are not diagnosed at birth are thought to be at risk to develop signs and symptoms of tethered cord syndrome as they grow. In a case series of 32 patients with lipomyelomeningocele, Segal et al. reported that these patients can uniquely present with asymmetric limb involvement but also with other well-established symptoms of tethered cord, such as back pain, scoliosis, foot deformities, weakness, paresthesias, and urinary symptoms [44].

Because of the distinctive clinical appearance of neonates with lipomyelomeningocele, imaging studies are often completed soon after birth. These often begin with neonatal spinal ultrasounds and/or X-rays. Spinal ultrasound will commonly demonstrate a vertebral arch defect and redundant subcutaneous fatty tissue. X-rays will often show the vertebral arch defect and may demonstrate thicker than normal lumbar soft tissue. If CT is undertaken, it will generally demonstrate focal enlargement of the spinal canal at the placode level and a hypodense fat-attenuated mass in

continuity with subcutaneous tissue. Due to radiation exposure and the inability to demonstrate fine anatomic detail, CT is not recommended as a routine imaging modality in the evaluation of a young child with suspicion of OSD.

As with most OSDs, MRI is the diagnostic study of choice for children with lipomyelomeningocele. Timing of initial MR imaging is provider dependent, but since these lesions are closed and covered with normal skin, urgent imaging after birth is not mandatory. In the series of OSDs published by O'Neill et al., the average age of initial MR imaging was 6 months [30]. Increasingly, high-volume centers obtain high-quality MRI studies in infants through specific protocols that combine evening scan times with feeding and swaddling immediately prior to initiating the study. In our experience, the ideal age for this protocol is 3–6 months, and the procedure is successful in approximately 75% of attempts. In this manner, general anesthesia can be avoided.

When investigating suspected OSD, MRI with axial and sagittal T1- and T2-weighted series will clearly demonstrate the lesion (Fig. 15.6). The surface of

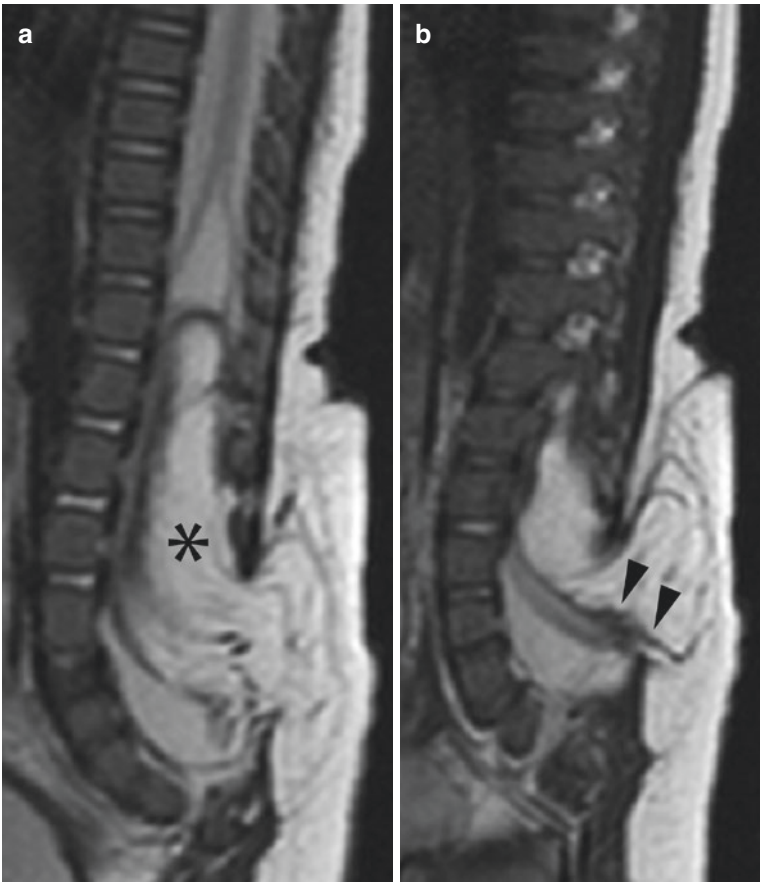

Fig. 15.6 (**a**, **b**) Sagittal T2-weighted MR images illustrate a lumbosacral lipomyelomeningocele with fat herniating into the spinal canal (black asterisk) and the neural placode extending through the dysraphic posterior elements attaching to the subcutaneous fat (black arrowheads)

the placode abuts the lipoma. In some cases, the plane between spinal cord and lipoma is rotated. While the lipomatous component of the lesion can transgress into the spinal canal, it does not invade the subarachnoid space. The dural sac is abnormally wide and the ventral subarachnoid space is expanded. Subcutaneous fat is continuous with the lipomatous element of the formation, and the entire lesion is covered with normal-thickness skin, causing a mound of skin-covered tissue in the lumbosacral region and often deviating the gluteal cleft.

Multiple other pathological entities are associated with lipomyelomeningocele. These include spinal arteriovenous malformations, Chiari 1 malformations, and more complex dysraphisms with multiple components [45–48]. There have been three case reports with a total of four patients demonstrating spinal AVM associated with lipomyelomeningocele [45–47]. Weon et al. presented a case of an intradural mass with high-signal intensity on both T1-weighted and T2-weighted images, intermingled with multiple signal-void structures, consistent with a lipomyelomeningocele associated with a spinal AVM [47]. Dhandapani et al. presented a case report of a complex spinal dysraphism including a myelomeningocele contiguous with a lipomyelomeningocele, centered on a Type 1 split cord malformation, with a Chiari 2 malformation and hydrocephalus [48]. Murakami et al. demonstrated that complex congenital spine malformations can be well characterized using heavily T2-weighted imaging. If scoliosis is present or suspected, the radiographic work-up can be supplemented by CT scans to define the 3-D bony anatomy [49].

Other Rare OSDs

There are several other OSDs that warrant description, as these can often be confused with or present alongside the more common OSDs presented above. Reviewing these diagnoses is, in part, a study in etymology but nevertheless important for diagnostic accuracy and facilitating clinical management and research of these lesions.

Less Common Lipomatous OSDs

Lipomyelocele is very similar to a lipomyelomeningocele and is evaluated and treated in much the same fashion. The difference between the two is that a lipomyelocele does not directly involve the dura, and therefore the “meningo-” is dropped from the name. On MRI, the neural-lipoma interface is located within the spinal canal (Fig. 15.7). The spinal canal may be enlarged by the lipoma, but the ventral subarachnoid space is normal, and the dura is not expanded. The literature specific to lipomyelocele is extremely limited, consisting predominantly of small series, case reports, and review articles dedicated to cataloging the various congenital spinal entities.

Less Common Non-lipomatous OSDs

A meningocele is a very uncommon OSD defined as a protrusion of dura through the spine and covered with the skin. Neural elements are not directly involved. These lesions are typically dorsal, in the lumbosacral spine and, despite the lack of

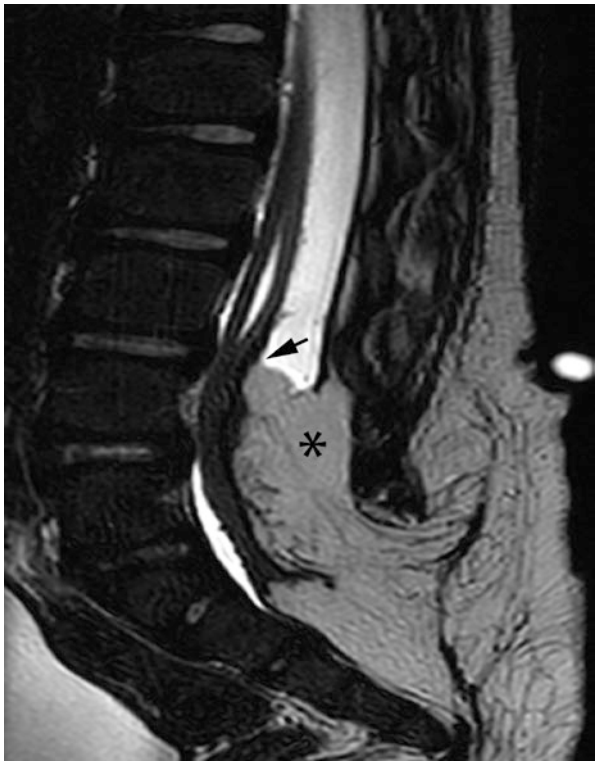

Fig. 15.7 Sagittal T2-weighted MR image demonstrates a lumbosacral lipomyelocele (aka lipomyeloschisis) with fat extending into the spinal canal through a dorsal dysraphic defect (black asterisk) and placode-lipoma interface that is entirely within the canal (black arrow)

neural tissue within the lesion, can be associated with a low-lying conus medullaris and tethered cord syndrome. Anterior meningoceles are exclusively sacral in nature and frequently associated with anorectal malformations.

A myelocystocele is a complex skin-covered lesion that must be distinguished from lipomeningoceles and meningoceles. Terminal and nonterminal myelocystoceles represent distinct entities.

A terminal myelocystocele is present exclusively in the caudal spine and includes a low-lying spinal cord with extrusion into the dorsal extraspinal space and fusion to the dorsal subcutaneous fat. The extruded cord or myelocele is trumpet-shaped, and the skin overlying the lesion is of full thickness. A terminal syrinx is also present and in continuity with the normal ependymal canal. These lesions are typically seen in association with the OEIS complex (omphalocele, exstrophy of bladder, imperforate anus, spinal defects).

A nonterminal myelocystocele is a complex skin-covered herniation of spinal tissue through a bony and dural spinal defect. These lesions are more commonly reported in the cervical spine but can be seen throughout the spine. In both cases, MRI is the diagnostic modality of choice.

Neurenteric Cysts

Neurenteric cysts (NECs) are a rare type of foregut duplication cyst that is a result of incomplete resorption of the neurenteric canal during fetal development. Cysts are usually intradural, extramedullary and ventrally located [50]. They are preferentially located in the cervical and craniocervical region. However, NECs have also been reported in the clivus, cavernous sinus, and throughout the spinal canal [51–53]. NECs are frequently associated with other vertebral anomalies, including Klippel-Feil syndrome, split cord malformation, spinal lipomas, DSTs, and tethered spinal cord. In a series of 13 adult and pediatric patients with a NEC, all but 1 presented with associated vertebral anomalies [54]. The authors further noted that children presented more commonly with cutaneous stigmata of OSD, whereas adults primarily presented with pain.

On CT, NECs typically present as a hypodense lesion with soft tissue attenuation and minimal-to-no contrast enhancement. Associated bony abnormalities, such as Klippel-Feil malformations and hemivertebrae, can be easily identified with this imaging modality.

On MRI, NECs are typically isointense on T1-weighted images and hyperintense on T2-weighted images, without true enhancement [55] (Fig. 15.8). It is important

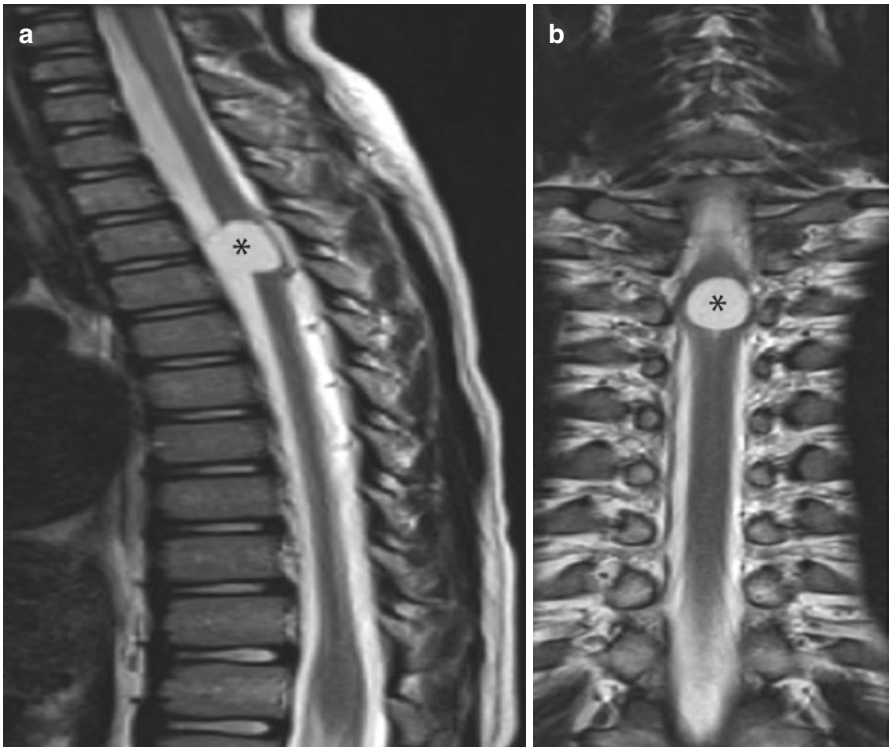

Fig. 15.8 (**a**) Sagittal and (**b**) coronal T2-weighted MR images reveal a neurenteric cyst of the upper thoracic spinal cord

to note that imaging characteristics of NECs commonly deviate from usual norms, based on cyst contents. The contents of NEC fluid sometimes undergo sedimentation, resulting in some regions demonstrating marked T1 hyperintensity and T2 hypointensity, due to the sedimentation of the more viscous contents [56]. Cysts can also hemorrhage, with subsequent imaging demonstrating increased susceptibility and blood products layering out within the cyst. Based on their own case report and a review of the literature, Jung et al. concluded that a finding of reversed signal between the T1- and T2-weighted images within a cystic mass should no longer be considered an atypical MRI finding in the context of spinal NECs [56].

There have also been numerous case reports published of NECs getting extremely large and mimicking other lesions, such as abscess [57] or cystic intramedullary tumor [58]. Theret et al. reported a 1-month-old who presented with a very large NEC that had eroded into the thoracic cavity [59].

These examples are discussed to emphasize that when imaging studies reveal the presence of a lobulated intradural extramedullary or an exophytic intramedullary cystic mass with discordant MR signals and variable enhancement, especially in association with anterior spina bifida or other vertebral anomalies, NEC should be a strong diagnostic consideration.

Split Cord Malformations

Split cord malformations (SCMs) are a group of extremely rare congenital malformations that involve duplication of some elements of the spinal cord. They are typically divided into Type 1 SCM and Type 2 SCM, previously referred to as diplomyelia and diastematomyelia, respectively.

Type 1 SCM is defined as two individual dural tubes, separated by an osseous or cartilaginous septum (Fig. 15.9). A bony spur is typically partial and attached to the dorsal surface of the vertebral body but can occasionally be attached to the ventral aspect of the posterior lamina [60]. Hydromyelia is common, vertebral anomalies at

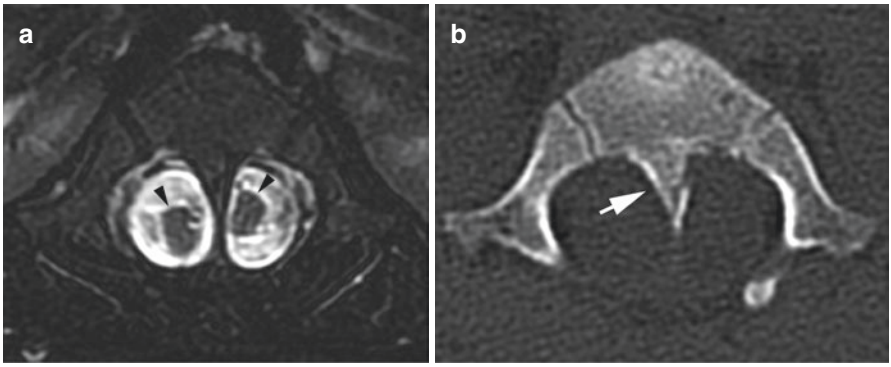

Fig. 15.9 (**a**) Axial T2-weighted MR image shows "splitting" of the spinal cord into two symmetric hemicords (black arrowheads), consistent with Type 1 diastematomyelia. (**b**) Axial CT image illustrates an osseous spur (white arrow) at that level. (Images courtesy of J. Blount)

adjacent levels are common, and patients are typically symptomatic, presenting with scoliosis and/or tethered cord syndrome [61].

Type 2 SCM is defined as single dural tube containing both hemicords. It is characterized by a single dural sac without an osseous spur or septum, though an intervening fibrous septum is commonly identified. The spinal cord can be divided but is sometimes incompletely divided with neural tissue communicating between the two hemicords. Hydromyelia and spina bifida may be present, but other vertebral anomalies are less common. Compared to Type 1 SCM, Type 2 SCMs are typically less symptomatic or sometimes even discovered incidentally.

MRI is the imaging modality of choice to diagnose and characterize the above lesions [62]. CT can be useful to define the bony anatomy, such as the bony spur that can be associated with Type 1 SCMs. There is also one report of fetal ultrasound used to diagnose split cord malformation, through the presence of an extra echogenic focus in the midline between the fetal spinal posterior elements [63].

Future Directions in Imaging of OSDs

There are many exciting new developments within the field of MRI, some of which are directly applicable to the imaging of OSDs.

As mentioned above, the development of protocols to avoid anesthesia for MRI in young children is an area that has seen rapid development. Among the primary reasons to avoid MRI in young children is the common need for general anesthesia. Several methods to avoid general anesthesia have been described: shortening the duration of the MRI scan to a "screening" MRI, using a "feed and sleep" or sleep deprivation protocol prior to an MRI [64], and using pre-imaging practice sessions or videos [65–68]. Some protocols use a combination of these techniques depending on the age of the patient, with "feed and sleep" protocols typically used in children under 4 years old and pre-imaging training for children over 4 years old [68].

In addition to developing protocols to facilitate the MRI experience, the acquisition of images is becoming faster. Longo et al. published a protocol that uses a simultaneous multi-slice technique with generalized autocalibrating partially parallel acquisition (GRAPPA) to shorten the duration of a lumbar spine MRI to 5 min. In an adult population, the sensitivity, specificity, and accuracy of the 5-min protocol were 92.3%, 100.0%, and 99.6%, respectively, for the clinically relevant findings [69]. With many fast T2-weighted protocols already in use for cranial MRI, we can expect fast MRI sequences of the spine to become more readily available.

MR diffusion-weighted imaging (DWI) and diffusion tensor imaging (DTI) techniques are also becoming more developed and are used to evaluate the health of the spinal cord [70]. Much of the current research is focused on acute traumatic spinal cord injury, but some groups are evaluating diseases such as multiple sclerosis, syringohydromyelia, and other pathologies. This may represent another avenue to evaluate the health of the distal spinal cord, such as in cases of occult tethered cord syndrome.

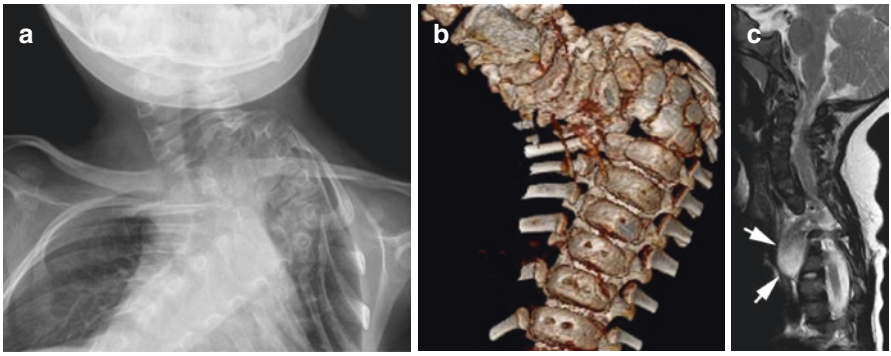

Fig. 15.10 (**a**) Chest X-ray image illustrates severe spinal deformity in a child with complex segmentation anomalies, as demonstrated by (**b**) 3-dimensional reconstructed CT image. (**c**) Sagittal T2-weighted MR image reveals a meningocele extending toward the mediastinum (white arrows). Additional MR imaging (not shown) revealed presence of neural tissue within the sac

Additionally, fetal MRI is becoming standard for prenatal diagnosis of fetal neural tube defects. Fetal MRI typically has enough anatomic detail to allow one to distinguish between closed and open spinal dysraphism [71–73]. This allows for prenatal treatment of open dysraphism and prenatal planning for closed defects that may not require immediate surgical intervention at birth.

Lastly, the combination of all the above imaging techniques mentioned can provide helpful clinical information. Children with complex spinal deformities are best imaged with multiple modalities to ensure a complete understanding of the anatomy before surgery, for example (Fig. 15.10).

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Urological Concerns of Occult Spinal Dysraphism/Tethered Cord

16

David B. Joseph

Introduction

Understanding of the ramifications of a tethered spinal cord has been perplexing to the pediatric urologist. The impact of imaging, spinal sonography, and MRI in neonates has led to an increase in identification of occult spinal dysraphism and the tethered cord. This has placed a greater burden on subsequent evaluation and management. The incidence and prevalence of occult spinal dysraphism remains unknown with simple incomplete fusion of the posterior lumbosacral elements note in 25–30% of children undergoing general urologic evaluation [1]. The natural history related to urologic symptoms for untreated occult spinal dysraphism is poorly defined as is the urologic benefit of operative detethering. The most accepted principle is that clinical symptoms and outcomes are highly variable regardless of the action taken with the tethered cord. The tethered cord following closure of a child with a myelomeningocele carries different ramifications than children found to have an occult spinal dysraphism. Adding to the confusion is the realization that etiology of occult spinal dysraphism has a variable impact on urologic function. The lack of a definitive urologic protocol for management of the occult spinal dysraphism places an even greater burden on the neurosurgeon when assessing the role for surgical detethering. The following will provide the urologic perspective of the evaluation and management of occult spinal dysraphism and tethered cord in hopes of providing a foundation for a multidisciplinary dialogue.

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Normal Bladder Development and Function

In order to place into perspective urologic symptoms of voiding dysfunction and the urologist's ability to objectively assess those symptoms, it is helpful to have a cursory understanding of functional development of the normal neonatal bladder. The fetal bladder transitions from a conduit to a reservoir at the end of the second trimester due to the maturation of the external urinary sphincter [2]. Neural pathways regulating bladder activity include sacral parasympathetic (pelvic) nerves, thoracolumbar sympathetic (hypogastric) nerves, and somatic (pudendal) nerves. Fetal voiding progresses through a transitional process based on active impulses traveling through these pathways that are continuously maturing [3]. In newborns and infants, there are gradual decrease in voiding frequency, increase in bladder capacity, and improvement in coordination of bladder contraction and external sphincter relaxation. Dyscoordinated neonatal voiding is normal and has been shown to be associated with a small functional bladder capacity and high voiding pressure [4, 5]. This is functionally different than bladder-sphincter-dyssynergia (detrusor-sphincter-dyssynergia) identified during urodynamic testing in older children [4]. It is appreciated that normal voiding dynamics in the neonatal age group accounts for incomplete bladder emptying and interrupted voiding (two voids within 10 min) due to dyscoordination at least through toilet training [5–7]. This concept must be appreciated when evaluating for bladder dysfunction [2]. It is presumed that regulation of neonatal bladder function is due to active impulses traveling through the neural pathways influenced by the cerebral cortex. Disruption of the pathway can occur with various manifestations of occult spinal dysraphism.

Urologic Pathophysiology of the Tethered Cord

The concept of the "tethered spinal cord" is inconsistently defined when reviewing the literature making it difficult to truly understand the pathologic consequences. Animal studies have shown that mechanical traction on neural elements reduces blood flow resulting in a reversible abnormality related to oxidative metabolism influencing abnormal functional bladder. Reversible changes occur with improvement in oxygenation inferring correction of a symptomatic tethered cord could do the same [1]. Translating this into clinical practice, however, is not a given. Factors related to neural dysplasia noted in caudal regression, split cord, and complex lipomas are not expected to have reversible impact on urologic symptoms following operative intervention. This brings to perspective the importance of identifying the etiology of occult spinal dysraphism and comparing specific lesions for consistent uropathologic variances. The problem for the urologist begins with identifying the patient that should be evaluated. It is intuitive that a symptomatic child regardless of age undergoes diagnostic testing. The dilemma relates to the need for, and extent of, assessment required in an asymptomatic child particularly the newborn or infant noted to have an occult spinal dysraphism.

Newborn/Infant

The symptomatic expression of urologic pathophysiology is a factor of developmental age. Three percent of normal newborns will have a cutaneous lesion, most of whom will not have clinically appreciated uropathology [8, 9]. Of newborns and infants with neuro-urologic deficits, many go unrecognized without invasive assessment. It is unknown if delayed presentation with the onset of symptoms at an older age will occur and, if it does, whether operative intervention at the time of occurrence will impact the outcome. Equally important is the fact that there is no evidence to support the benefits of early intervention in this group. Newborns with sacral (caudal) agenesis are at a high risk for persistent urogenital pathophysiology regardless of treatment particularly when associated with complex syndromes such as VACTERL, OEIS, and LUMBAR [10].

The struggle for the urologist becomes identifying who benefits from evaluation as it relates to cost-effective utilization of resources and potentially subjecting newborns to unnecessary invasive investigation. The end result of indiscriminative assessment of all occult spinal dysraphism becomes problematic with the burden placed on the neurosurgeon who now must balance the risks and benefits of operative intervention. This is where an initial multidisciplinary approach between the neurosurgeon and urologist has strong practical benefits.

Dias and Partington stratified cutaneous spinal lesions into low- and high-risk groups based on the position and appearance of the occult spinal dysraphism and association of MRI findings [11]. Low-risk lesions include flat hemangioma, non-midline defect, forked gluteal cleft, coccygeal pit, and asymmetric gluteal cleft. High-risk lesions are described as hypertrichosis, infantile hematoma, limited dorsal myeloschisis, dermal sinus track, subcutaneous lipoma, caudal appendage, midline pedunculated swelling, and sacral agenesis [11]. While strong evidence is lacking, it is practical from a urologic perspective to consider limiting the newborn and infant assessment to Dias' high-risk group.

Assessment

Imaging

The lack of ossification of posterior sacral elements in the newborn allows for ultrasonographic evaluation of the spinal cord through 3 months of age in a cost-effect fashion [12]. The ready availability of ultrasonography brings with it the responsibility to limit needless screening [13]. The conus terminates below L2 in only 13%, 11%, and 5%, respectively, in the first, second, and third months of life [14]. Therefore termination below the L2 landmark is used by the urologist to justify further investigation. MRI assessment greatly enhances spinal anatomic evaluation but comes with the need for sedation in most cases. Newer "feed and swaddle" techniques may overcome the recent neurotoxic concerns of newborn anesthesia and the expense of advance technology [15–17].

Urodynamics

The primary diagnostic test of neuropathology is the urodynamic study (Fig. 16.1). While invasive, this study provides objective, concrete, reproducible information regarding dynamic bladder parameters. The goal of urodynamic testing is two-fold: identifying the neonate, infant, and child who may have neurogenic bladder dysfunction and recognizing the neonate and infant who might be at risk of upper urinary tract deterioration due to abnormal bladder dynamics. The pediatric urodynamic study does require additional considerations over that of the adult study, but it can produce meaningful data when performed in a meticulous fashion, adhering to principles based on specific characteristics of the infant and child such as rate of filling [18, 19]. The newborn urodynamic study provides lower urinary tract data that can be used in support of operative neurosurgical intervention and provides an important baseline for information when assessing postoperative outcome and concern for future retethering [18, 20, 21].

Simultaneous assessment of bladder dynamics and sphincter activity is undertaken through the cystometrogram and electromyography (Fig. 16.2). Invasive catheters are placed transurethral and transrectal in order to assess bladder compliance (the ability to fill the bladder at low pressure), bladder stability (identifying overactive neurogenic contractions), leak, and voiding pressure. The external urinary sphincter is assessed with placement of either perineal patch electrodes or needle electrodes to record the sacral cord reflex and coordination of the external urinary sphincter and bladder activity during filling and voiding. Patch electrodes monitor generalized pelvic floor activity; needle electrodes provide more precise urinary sphincter activity and potential of denervation. The EMG wires are inserted with needles and are momentarily painful in sensate patients. This “pin prick” can be utilized to assess for a perineal sensory deficit.

Sensory deficit, decreased bladder compliance, overactive contractions, and dyscoordinated voiding are objective urodynamic parameters exacerbated by a

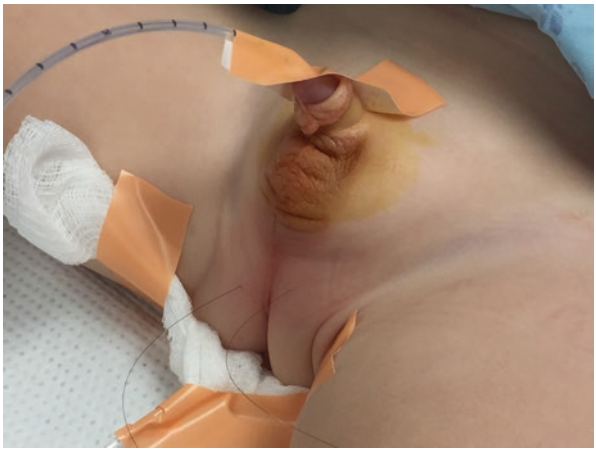

Fig. 16.1 One-year-old boy with urethral catheter for bladder pressure, rectal catheter for abdominal pressure, and paired wire perineal EMG electrodes

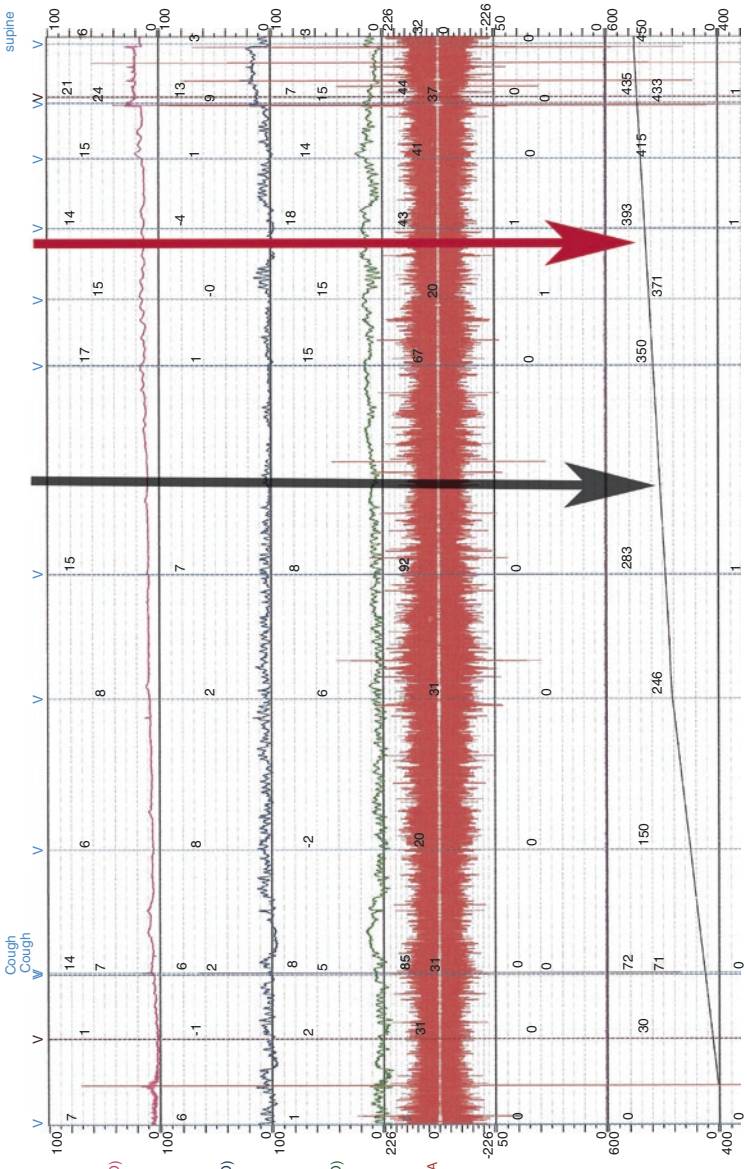

Fig. 16.2 Urodynamic cystometrogram tracing. (**a**) Eight-year-old girl continent on intermittent catheterization. Black arrow represents bladder pressure at predicted bladder capacity for age, 300 mL. Red arrow is bladder (detrusor) leak point pressure of <20 cm H_2O occurring beyond her predicted bladder capacity. Characterized as a safe bladder. (**b**) Purple arrows represent neurogenic overactive bladder contraction. Blue arrows show simultaneous sphincter activity. This represents bladder (detrusor) sphincter dyssynergia resulting in high pressure elimination of urine. Characterized as a hostile bladder. pves = bladder pressure, pabd = abdominal pressure, pdet = pves-pabd. Represents calculated detrusor (bladder) pressure. Eliminates external bladder pressure from movement, cough, crying, or other forces that generate abdominal force that could be reflected in bladder pressure

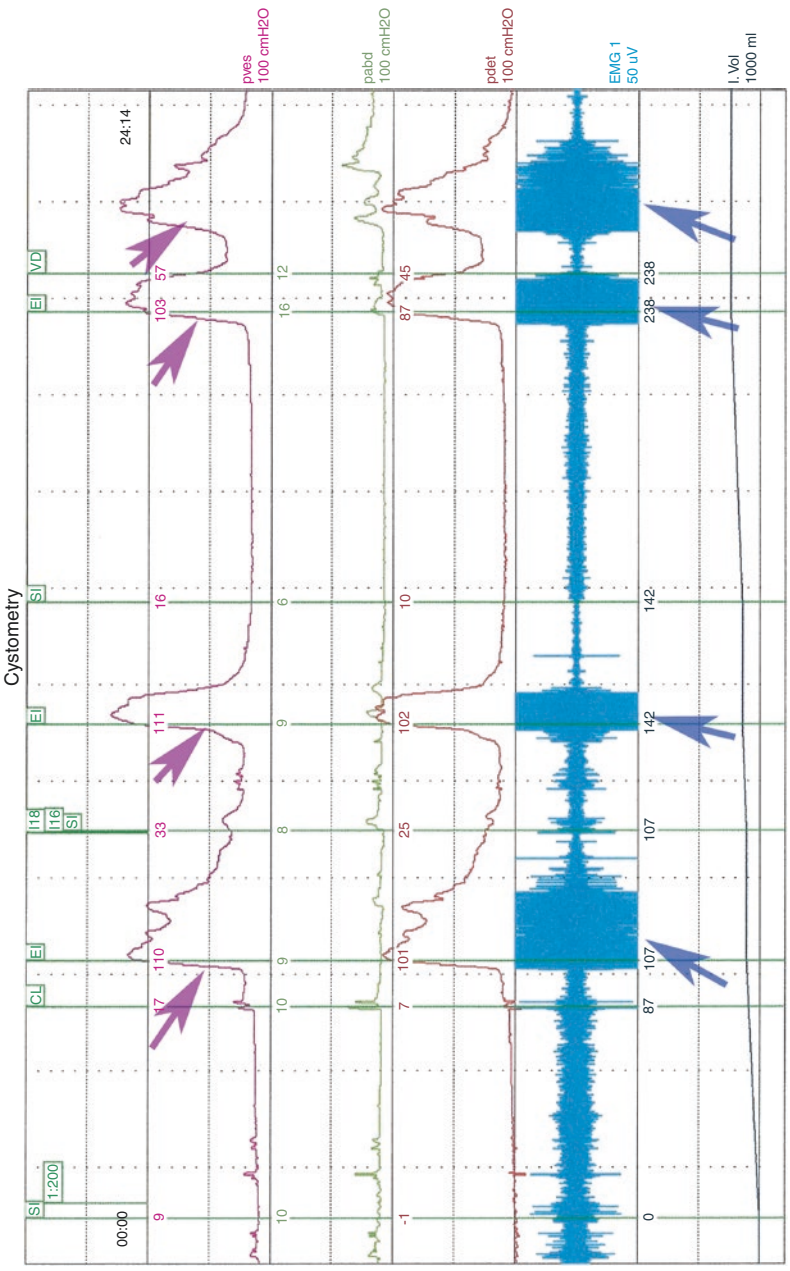

Fig. 16.2 (continued)

Table 16.1 Urodynamic classification

Normal
Capacity as predicted by age
Compliance <15 cm H_2O
Normal voiding contraction
Minimal post void residual
Safe
End-filling pressure <25 cm H_2O
Bladder (detrusor) leak point pressure <25 cm H_2O
Intermediate
Neurogenic bladder overactivity
Reduced compliance
End-filling pressure 25–39 cm H_2O
Bladder (detrusor) leak point pressure 25–39 cm H_2O
Hostile
Neurogenic bladder overactivity
Bladder (detrusor) sphincter dyssynergia
End-filling pressure >40 cm H_2O
Bladder (detrusor) leak point pressure >40 cm H_2O

tethered cord. Neurogenic bladder over activity is a common abnormal parameter associated with the tethered cord [22]. Because of normal neonatal bladder development, critical assessment is required to differentiate the neurogenic overactive bladder from the normal dyscoordinated voiding response of the normal neonatal bladder. Typically, neurogenic overactivity is noted with a repetitive sinusoidal pattern over a short period of time. Bladder-sphincter-dyssynergia (detrusor-sphincter-dyssynergia), external sphincter activity simultaneously recorded during a voiding contraction, is also characteristic of spinal cord tethering. Adding a video component to the urodynamic study can enhance dynamic bladder assessment allowing for direct fluoroscopic visualization of the bladder, bladder neck, sphincter activity, vesicoureteral reflux, and post-void residual. Recently urodynamic tracings have been classified as normal, safe, intermediate, and hostile based on specific parameters (Table 16.1). The intent for standardizing specific aspects of the urodynamic report was to assist with comparative analysis of abnormal parameters across institutional centers providing a foundation for consistent treatment and establishment of evidence-based guidelines [23].

Most important direct communication with the patient's neurosurgeon is required to place abnormal urodynamic parameters into context with the clinical symptoms and physical findings.

Assessment

The urologic assessment of children with a tethered cord must be individualized. However, generalized themes can be followed based on categorization of the child as it relates to age, physical findings, and symptoms.

Newborn with Urogenital or Anorectal Anomalies

A newborn with urogenital or anorectal anomalies typically has an obvious physical finding encompassing a spectrum of abnormalities from an imperforate anus to the cloacal exstrophy complex of omphalocele, exstrophy, imperforate anus, and spinal defects (OEIS syndrome). By definition, this group of patients requires spinal imaging to assess the impact of their spinal defect. While spinal ultrasonography can be readily obtained for screening, spinal MRI is the most definitive. Urologic assessment begins with establishing upper urinary tract status; there is a greater incidence of having a solitary kidney. Renal ultrasonography provides for rapid baseline appraisal and an effective modality for following renal changes during maturational development. Lower urinary tract dynamic testing must wait closure of the bladder exstrophy. The syndrome encompassing vertebral anomalies, anorectal defects, cardiac defects, tracheoesophageal fistula, renal abnormalities, and limb deformity (VACTERL) by definition of the spinal and renal involvement also requires assessment of the spinal cord and upper urinary tract in a similar fashion. These newborns have an intact bladder and therefore benefit from urodynamic testing, but the procedure can be technically challenging based on the severity of the urorectal defect and the ability to pass the required urodynamic catheters.

Children presenting with only an anorectal malformation may not have the obvious physical stigmata of a tethered cord but nevertheless should undergo spinal cord screening with ultrasonography due to the 10–53% reported prevalence of occult spinal dysraphism [24]. The incidence of a spinal defect increases when the imperforate anus is above the levator ani muscle [1]. Urologic assessment is initiated with renal sonography. Urodynamic testing for baseline function is reserved for newborns with a confirmed occult spinal defect with tethered cord on imaging.

Sacral agenesis has a typical appearance of a low gluteal crease and a flattened buttock. The combination of pelvic imaging and spinal sonography typically will suggest when a neurologic defect is present. Urologic assessment requires renal sonography and urodynamic testing. Any bladder and/or sphincter dysfunction present in the neonatal period is established. Bladder dysfunction typically does not progress nor is it improved over time supporting a conservative nonoperative neurosurgical approach [1].

Newborns and Infants with Cutaneous Stigmata

Occult spinal dysraphism is associated with a cutaneous marker in 80% of newborns and infants [8, 9]. On the other hand, 3% of healthy newborns have noticeable cutaneous lesions. The significance of the cutaneous lesions differs, and the infant rarely presents with noticeable urologic dysfunction. As categorized by Diaz and Partington, midline cutaneous lesions raise variable levels of concern [11]. Sanani et al. found the incidence of tethered cord to occur in 27% when a spinal dimple overlies the sacrum where a similar appearing dimple overlying the coccyx had

tethering in 8% [25]. While this paper has the limitations related to its retrospective review and likely over reports tethering in coccygeal lesions, it does support the predictive ability of location of the cutaneous defect to assist in determining clinical significance. Using that principle then helps limit needless assessment of majority of low spinal defects. From a urologic perspective, initial assessment should be confined to documenting the upper urinary tract status with renal sonography. Urodynamic testing is reserved for infants confirmed to have occult spinal defect and or neurologic deficits of the lower extremity.

Symptomatic Dysfunctional Voiding in Toddlers and Young Children

Toddlers older than 3.5 years who have failed to gain urinary and/or bowel control or the older adolescent who has achieved urinary continence and subsequently regresses to an incontinent state should undergo renal/bladder screening with ultrasonography and plain film imaging of the spine. Selected children should be considered for urodynamic testing. When neurologic dysfunction is identified, a conversation should be undertaken with a neurosurgeon to discuss the need for a spinal MRI.

Neurosurgical Intervention

Data on the natural history related to urologic dysfunction of occult spinal dysraphism is limited making it difficult to dogmatically state detethering of the spinal cord from a urologic perspective is beneficial. Justification for neurosurgical intervention weighing risks and benefits is easier in the symptomatic older child with de novo or progressive voiding dysfunction. Favorable results are manifested by symptomatic and/or urodynamic improvement or with stabilization of neurologic pathology. However, this is not always objectively achieved [26–28].

Asymptomatic Occult Spinal Dysraphism with Tethering

Understanding that bladder dysfunction may not be reversible in some children with occult spinal dysraphism who transition into dysfunctional voiding heightens interest into the ability to predict which asymptomatic child with normal urodynamic function is at risk of developing neuropathology. The answer is likely buried within the underlying pathology. While the asymptomatic child with a low-lying conus and thick fatty filum may be a low risk for urologic deficits, if surgical intervention has a lower risk for morbidity, treatment of the tethered cord could be justified. On the other hand, a complex lipoma places the asymptomatic child at a distinct risk for the onset and progression of bladder dysfunction, but the complexity and morbidity

of neurosurgical intervention may be greater than the urologic dysfunction, and the balance does not warrant intervention [29, 30]. With the difficulty interpreting secondary spinal cord tethering on MR imaging, consideration should be given to obtain preoperative baseline urodynamic testing, even in the asymptomatic child if neurosurgical intervention of the occult spinal defect is undertaken. A baseline urodynamic study provides the foundation for comparison of dynamic bladder changes overtime, often an early objective indicator of symptomatic tethering. The presence or absence of urodynamic changes can help guide the neurosurgeon when assessing the need for subsequent intervention particularly in difficult cases [2].

"Tight Filum" or Occult Tethered Cord Syndrome

Pediatric urologists are frequently confronted by the symptomatic child with voiding dysfunction and documented urodynamic pathology but without MRI evidence of spinal cord tethering. This has been described as the "tight filum" or occult tethered cord syndrome [31, 32]. The limited morbidity and potential value of intradural sectioning of the normal filum has been supported by subjective symptomatic improvement of bladder symptoms, but objective urodynamic data pre- and post-intervention are limited and incomplete [33–35]. When available, urodynamic assessment has supported improvement with voiding dysfunction particularly daytime incontinence in 50–75% of patients following filum sectioning [35–37]. It is appreciated that limitations have occurred with prior studies, and further neurosurgical-urologic multidisciplinary prospective studies are required. Positive results have recently been countered by Steinbok et al.; the authors report on a pilot study revealing no benefit from sectioning of the filum on lower urinary tract dysfunction [38].

Complex Lipomyelomeningocele

Complex lipomyelomeningocele is appreciated by the urologist to carry significant morbidity related to bladder dynamics and voiding dysfunction. When untreated, there is data to support loss of bladder function in 40% over 10 years [25, 28, 29]. However there is the understanding that neurosurgical intervention is difficult and remains controversial due to the complexity of the lesion and risk for operative morbidity from re-tethering and neurological compromise in 5%. This additional morbidity may be worse than originally present giving the neurosurgeon pause when considering initial intervention [39–44]. Studies supporting a urologic advantage for surgical intervention are limited by their retrospective approach and inconsistent patient selection [31, 40, 45–48].

A conservative approach is reasonable for the complex lipomyelomeningocele particularly when the patient is asymptomatic [1]. Surveillance should include baseline urodynamic testing, and while not evidence based, routine follow-up particularly through the younger ages can be justified to identify asymptomatic early objective

urodynamic changes supporting an adverse effect of tethering. Once clinical deficits occur, recovery is limited regardless of neurosurgical intervention [26, 49].

Rare Spinal Malformations

Split cord, limited dorsal myeloschisis, dermal sinus track, and terminal myelocystocele are all rare conditions with minimal data to support the urologic benefits of neurosurgical intervention related to the onset of symptoms or improvement of preexisting dysfunction. The exceptions are treatment of the dermal sinus track prior to infection in order to limit pathologic sequel and the association of the terminal myelocystocele with OEIS or cloacal exstrophy. From a urologic perspective, operative intervention on the tethered cord is reasonable, but surveillance from a urologic perspective could be justified based on the fact that the anatomic urinary malformation impacts bladder dynamics regardless of any neurologic compromise. Understanding this might allow neurosurgical intervention to be based on the association of lower extremity pain or adversity of motor function.

Outcome

Improvement in dysfunctional voiding or abnormal objective urodynamic parameters is influenced by multiple factors beginning with the type of occult spinal dysraphism followed by age of the patient, severity of the dysfunction, and underlying associated uropathology. A major limitation when comparing outcome papers is the lack of continuity in defining the patient regarding primary or secondary tethering, the type of underlying lesion, and underlying symptomatology. To no surprise, comparative data regarding surveillance are limited due to ethical concerns for observation and the small numbers of patients that prevent any realistic prospective study. Case reports have supported neurologic improvement without intervention [50].

Age may play a role regarding benefits of surgery with support for improvement in abnormal urodynamic parameters identified when intervention was undertaken early in infants [36, 40, 51–53]. Frainey et al. reviewed continence patterns in patients with an average follow-up of 7 years following tethered cord surgery; overall, 80% were voiding and continent and 20% incontinent or on CIC. Patients who were continent prior to surgery remained continent after surgery, while only 45% of incontinent patients became continent following surgery [53–55]. Patients with bladder dysfunction as defined by abnormal urodynamic parameters have also shown a highly variable pattern for improvement following operative intervention of the tethered cord [20, 36, 49, 52, 56–62]. Yener et al. evaluated the effect of untethering in their patient population assessing the impact on symptoms and urodynamic parameters. They documented overall improvement independently with both following neurosurgical intervention. Interestingly, the authors could not show a correlation between improved symptoms and improved urodynamic parameters in the same patient [22].

Follow-Up

Long-term follow-up is critical particularly for symptomatic patients and those that have undergone spinal cord surgery. Tarcan et al. reviewed a small group of infants before and after detethering. They found over 9 years that 32% of children showed progressive neurological deterioration with the adverse changes all occurring before the age of 6 years [63]. That supports the current philosophy on following patients. Infants should be followed at a minimum of every 6 months with renal/bladder sonography until they have gained urinary control or the age of 3 years. Thereafter yearly assessment is recommended when voiding is normal and otherwise asymptomatic. The necessity of repeating the urodynamic study is influenced by the baseline study, predicted risk of deterioration due to the lesion, and history of neurosurgical intervention. Children under the age of 6 years have the greatest potential for change, and it is reasonable to repeat the urodynamic study yearly through the age of 3 years. After that age, urodynamic testing is then performed as needed based on any change in the patients' clinical status.

Ambulatory children with urinary continence should be followed with renal/bladder sonography on a yearly basis at least through the teen years. There is a paucity of evidence related to urologic outcomes in adults with occult spinal dysraphism. Veenboer et al. performed a meta-analysis on patients 18 years-old and older. They found only seven papers that met their adult criteria. Outcome analysis within these reports were highly variable leading the authors to recommend lifelong urologic follow-up [62].

Conclusion

Urologic manifestations of occult spinal dysraphism are variable with limited evidence-based data to support definitive surveillance or operative intervention of the tethered cord. From a urologic perspective, upper urinary tract monitoring can easily be undertaken with ultrasonography. Lower urinary bladder dynamics are best assessed through invasive urodynamic testing. Baseline urodynamic testing should be considered in any neurosurgical patient prior to intervention when possible and those who are followed under surveillance. Subsequent urodynamic studies can be performed to investigate progression of the pathology or the need for intervention due to suspected postoperative tethering. Most importantly, patient care is enhanced with having an open dialogue between the neurosurgeon and urologist regarding present status and possible concerns allowing for a multidisciplinary approach to care.

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Interface Between Occult Spinal Dysraphisms and Myelomeningoceles

17

Irene Kim and W. Jerry Oakes

Introduction

Spinal dysraphism encompasses a broad spectrum of congenital spinal anomalies, from open myelomeningocele (MMC) to simple thickening of the filum terminale. Spina bifida can also refer to incomplete union of the dorsal bony elements. This is a common finding on routine radiographs and is infrequently associated with surgically significant intradural pathology. While there are several discrete, well-defined entities, such as MMC, lipomyelomeningocele, neurenteric cyst, split cord malformation (SCM), etc., there are also more complex spinal dysraphisms that are not as well defined and involve two or more aforementioned entities [1, 2]. Thus, it may be better to consider spinal dysraphism as a continuous spectrum rather than as a group of discrete spinal malformations.

Moreover, there have been numerous reported cases of patients with more than one expression of spinal dysraphism [2–5]. These can occur at separate locations with intervening normal spinal elements, or at the same level, or both. While uncommon overall, one of the more frequently seen associations is SCM and MMC or the presence of both an open and a "closed" defect [1, 6, 7].

Pang's unified theory posits that the embryogenesis of SCMs originates from a basic ontogenic error at the time of primitive neurenteric canal closure, the formation of an aberrant or accessory neurenteric canal through the midline embryonic disc resulting in a focal "split" of the notochord and overlying neural plate. He classifies SCMs into two types: type I, in which each hemicord lies within its own dural sleeve and the two hemicords are separated by a bony septum, and type II, in

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which the two hemicords lie within a single dural sleeve and the two hemicords are separated by a fibrous septum [8]. Please see Chap. 12 for more detail on SCMs. The presence of both SCM and MMC is most suggestive of a developmental error during the 3rd to 4th week of embryogenesis [1, 9].

The reported incidence of SCM with MMC is variable. Among patients with any spinal dysraphism, the presence of both SCM and MMC has been reported in 3–15% of patients [1, 10]. In a series of patients with MMC, 6–13% of patients were observed to have concomitant SCM [6, 7, 11]. Conversely, in a series of patients with SCM, rates of patients with concomitant MMC vary widely from 17% to 42% [12–15].

Coexistent SCM and MMC occur much more commonly in type I SCM. Both Iskandar et al. and Kumar et al. found that 75% of patients with both SCM and MMC had type I SCM and 25% of patients had type II SCM [1, 7]. Similarly, Ansari et al. found 79% of patients had type I SCM and 21% of patients had type II SCM [6]. Erşahin found that only 1 of 24 patients had a type II SCM (96% type I SCM, 4% type II SCM) [11].

Although SCM occurs more commonly in females, there is no definite gender predilection for concomitant SCM and MMC [6, 12–14]. Iskandar et al. reported a heavy female predominance in their series (90% female, 10% male) [7]. However, Ansari et al. noted the patients in their series were 55% female and 45% male, while Kumar et al. reported nearly the exact opposite, 44% female and 56% male [1, 6].

In patients with coexistent SCM and MMC, the relationship of the SCM to the MMC is variable. The SCM can occur proximal to, at the level of, or distal to the MMC. Most commonly, the SCM is within one or two vertebral levels of the MMC, usually rostrally (Fig. 17.1) [1, 7, 11, 14, 16, 17]. A smaller but still significant proportion of patients (reported rates of 25–52%) have the SCM at the level of the placode [1, 6, 7, 12]. SCMs that are caudal to the MMC are relatively uncommon, with reported rates varying from 0% to 30% [1, 7, 11, 14, 18].

When the SCM is at the level of the neural placode, the MMC can involve one or both hemicords. Both hemicords can be involved if the MMC is present at the rostral or caudal aspect of the split. The presence of the MMC on one hemicord without involvement of the other hemicord is known as hemimyelomeningocele or hemimyelia.

Hemimyelomeningoceles are rare and infrequently discussed in the published literature [19–21]. Iskandar et al. reported that all six patients (100%) with SCM at the level of the MMC had hemimyelia, which constitutes 40% of patients with SCM and MMC [7]. Erşahin reported that seven of ten patients (70%) with SCM at the level of the placode had hemimyelomeningocele (21% of all patients with SCM and MMC) [12]. Ansari et al. reported that 4 of 33 (12%) with SCM and MMC had hemimyelia—3 of 17 patients (17.6%) of patients with SCM at the level of the MMC and 1 of 10 patients (10%) with SCM distal to the placode [6].

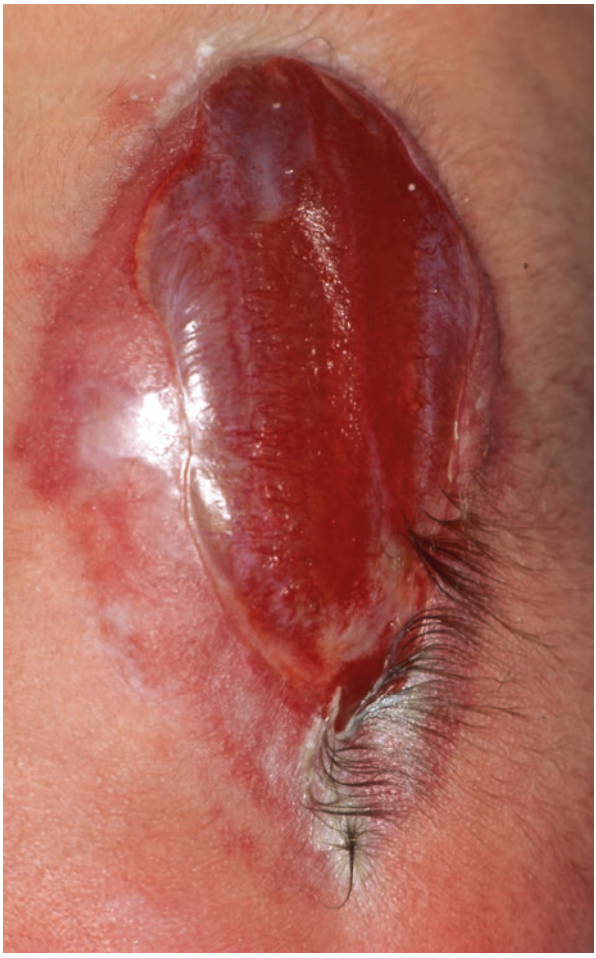

Fig. 17.1 Clinical photograph of a newborn shortly after birth with a typical appearing myelomeningocele. However, close inspection demonstrates focal hirsutism in the right inferior portion of the skin. Careful neurologic examination reveals a two segment difference in neurologic function of the lower extremities, with the left leg having normal neurologic function and the right leg having only hip flexion

Clinical Presentation

All patients with SCM and MMC come to neurosurgical attention at birth due to the open MMC, even if the existence of the SCM is not recognized at that time. The presence of cutaneous stigmata, particularly hypertrichosis, should raise suspicion for the presence of SCM (Fig. 17.2). Please see Chap. 4 for more on cutaneous stigmata. However, Pang et al. observed that patients with SCM and MMC were less likely to have cutaneous findings aside from the MMC sac compared to their counterparts with SCM alone without MMC. He suggests that these stigmata, which are minor aberrations in the development of the surface ectoderm, are overshadowed by the chaotic changes that occur in the surface ectoderm due to the non-neurulation of the underlying neural plate in MMC [13].

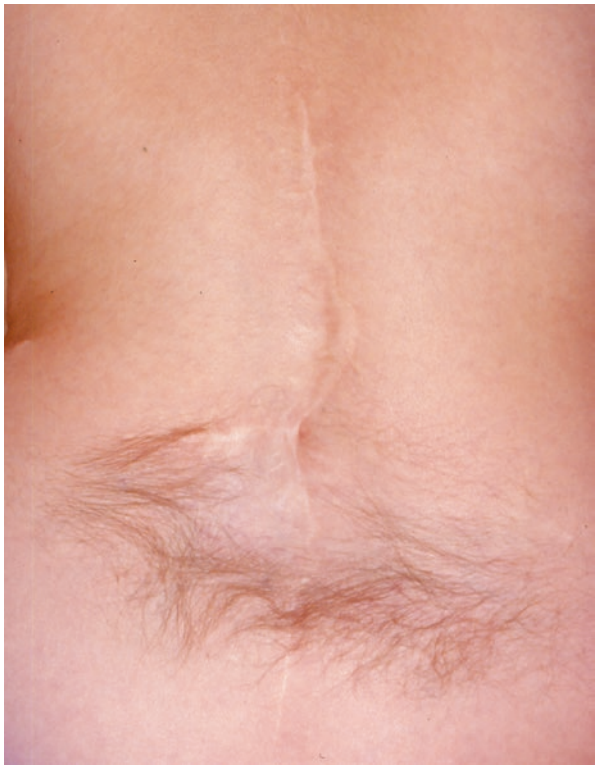

Fig. 17.2 Clinical photograph of the skin over the lumbar spine showing a well-healed myelomeningocele closure incision but focal hirsutism immediately below the scar. This 12-year-old presented to our spina bifida clinic with a dramatic worsening of function in his good left leg and progressive loss of previously normal bladder control. Evaluation disclosed a split cord malformation, where the myelomeningocele had been repaired but the fixation of the unrecognized hemicord by a thickened filum terminale had not been appreciated

Patients with hemimyelomeningocele can sometimes be identified by a slightly paramedian location of the MMC [17]. More commonly, they present with an asymmetric lower extremity neurologic exam. Typically, neurologic function is worse in the lower extremity ipsilateral to the hemimyelomeningocele by two spinal levels [13, 17, 20, 22]. However, Pang reported that in those patients with hemimyelomeningocele as well as asymmetric cord splitting, neurologic function is poorer in the lower extremity ipsilateral to the smaller, atrophic hemicord [13].

Unlike patients with MMC, patients with hemimyelia usually have intact bladder and bowel function, since the contralateral sacral nerve roots originating from the hemicord without the hemimyelomeningocele are not involved and therefore unaffected. Unilateral sacral nerve function is thought to be sufficient for maintenance of urinary and bowel continence [23–26]. In the absence of another expression of spinal dysraphism or asymmetric cord splitting with a smaller, contralateral hemicord, patients with hemimyelia should be able to maintain urinary and bowel continence.

While preoperative imaging with magnetic resonance imaging (MRI) or computed tomography (CT) may be useful to better understand the anatomy and to identify the presence of SCM or any other expression of spinal dysraphism, it is not necessary.

Management

All patients with SCM and MMC will undergo MMC repair shortly after birth. If not already identified preoperatively, SCM may be identified intraoperatively by the presence of a bony medium septum. Since SCMs most commonly occur within one or two vertebral levels of the MMC, we routinely incise the last intact spinal lamina during every MMC repair at our institution to carefully inspect for a possible SCM.

Meningocele manqué (MM) may also indicate the presence of SCM [27, 28]. Initially described by Lassman and James, MM are aberrant nerve roots and fibrous bands that tether the spinal cord to the inner dorsal aspect of the dura. Please refer to Chap. 13 for more detail about the ongoing discussion regarding the precise definition and classification of MM. These tethering tracts typically arise at the dorsal medial aspect of the hemicord and frequently terminate at the inner dorsal aspect of the dura but can extend further and terminate at the ventral aspect of the overlying lamina [27–29]. Care must be taken to meticulously dissect free and divide or remove these nerve roots and bands to prevent tethering of the spinal cord.

If the presence of both MMC and SCM is recognized pre- or intraoperatively, they can both be treated during the primary repair. The technical details of operative MMC repair will not be reviewed here, and details regarding operative management of SCMs can be found in Chap. 12.

Operative management of hemimyelia is an extension of MMC repair (Figs. 17.3, 17.4, and 17.5). Pang describes two different types of hemimyelomeningoceles. In the first, more common type, the involved hemiplacode is carefully dissected free from the dorsal dura and repaired in the same manner as a routine MMC closure. The contralateral hemicord is not visualized due to the median septum and is not involved in the open myelomeningocele sac. The two neural tubes are almost always rotated in the coronal plane. The more dorsal tube has the hemimyelia, and the "unaffected" hemicord is tucked underneath. This anatomy can be difficult to identify and understand unless one is deliberately looking for it.

Once the placode is reapproximated and the second dural sac appreciated, the rotated bony septum and its dural sleeve should be removed to expose the "hidden"

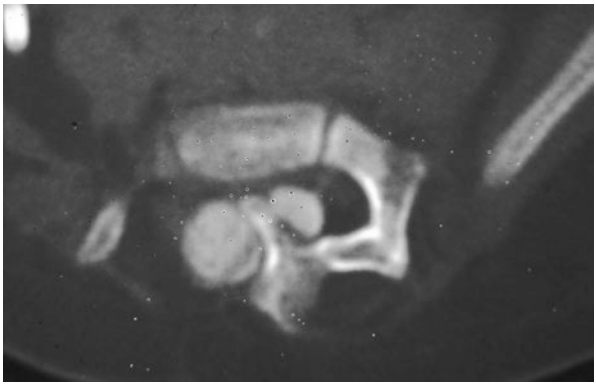

Fig. 17.3 CT myelogram of the lumbosacral spine demonstrating a bony median septum and a bony defect over the more superficial hemicord. The other hemicord is tucked up under the bony median septum in a separate dural sac

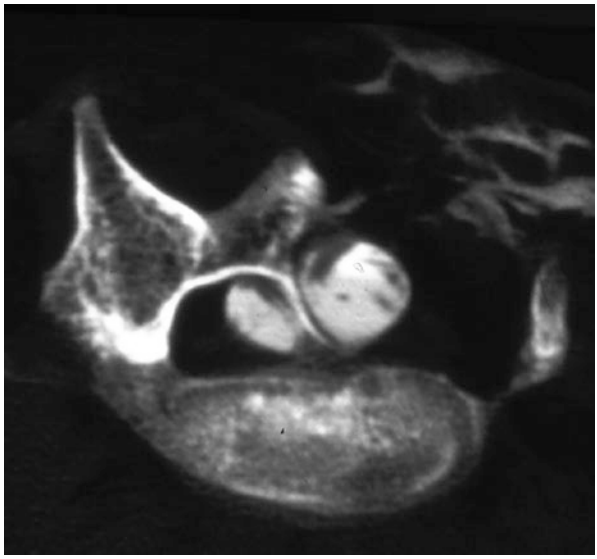

Fig. 17.4 CT myelogram of the lumbosacral spine again demonstrating two dural sacs separated by a bony median septum. It is easy to appreciate how only one dural sac would be seen at the time of the myelomeningocele closure. Careful inspection and recognition during surgery are important so that any tension on the functioning "hidden" neural elements is relieved by section of the filum terminale

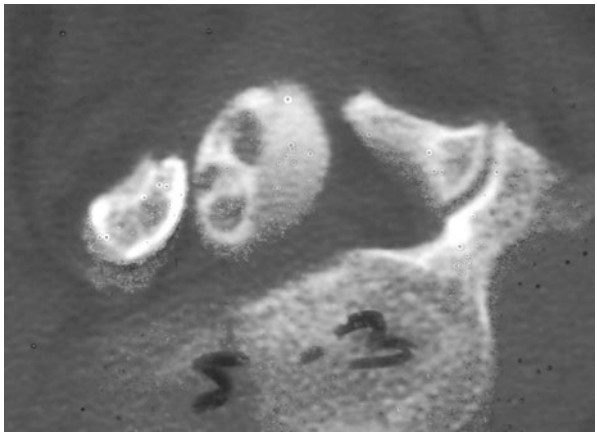

Fig. 17.5 CT myelogram of the lumbosacral spine again showing rotation of the two hemicords with little evidence of a bony septum at this level

cord. This portion of the cord is almost always fixated by its filum terminal and should be sectioned to avoid secondary neurological loss.

In the second type, a thin stalk of neural tissue arises from the involved hemicord, enters the myelomeningocele sac just rostral to the bony septum, and fans out over the inner surface of the sac. This stalk is incised flush to the dorsal surface of the hemicord, and the myelomeningocele sac is then removed. The remainder of the involved hemicord otherwise continues caudally in the spinal canal until it joins with the contralateral, uninvolved hemicord [8, 13].

Without careful inspection, only the MMC is repaired at birth because the SCM goes unrecognized. These patients subsequently become symptomatic in a delayed fashion. Clinical symptoms are similar to that of spinal cord tethering. Progressive

lower extremity weakness, sensory deterioration, and bladder dysfunction are the most common findings [1, 6, 7, 13]. Workup with MRI is warranted, and it is at this time that the SCM is usually identified. Operative management for treatment of the SCM is indicated.

Outcomes

There is not much in the published literature regarding surgical outcomes for patients with SCM and MMC, even less on long-term outcomes or on patients with hemimyelia. The majority of the patients appear to tolerate surgery well without deterioration in their preoperative neurologic status, and a few appear to have some slight improvement in the neurologic status [1, 17, 18, 20]. Kumar et al. noted that 5 of 16 patients developed pseudomeningocele, 2 required surgical intervention, and 3 were managed conservatively. They also reported a single case each of wound dehiscence, meningitis, and ventriculitis [1]. Iskandar et al. reported that 3 of 20 patients (15%) eventually required reoperation for secondary spinal cord tethering due to scar tissue [7].

Conclusion

SCM with MMC is among the more common associations seen in complex spinal dysraphism. True hemimyelia, with the MMC arising from one hemicord, is rare and usually presents with asymmetric lower extremity neurologic function. Because most SCMs occur within one level of the MMC, it is important to look for SCM during the initial MMC repair. We recommend opening the last intact spinal lamina, just rostral to the placode. Identifying a SCM, if present, and treating the SCM at the time of the MMC repair not only prevents a second operation; it also avoids the natural history of SCM, which is that of progressive neurologic deterioration [7].

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Associations of the Occult Spinal Dysraphisms

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Introduction

Occult spinal dysraphism (OSD) denotes a group of anomalies resulting from errors during embryogenesis with midline mesenchymal, neural, and ectodermal elements failing to form properly. OSD was initially classified by von Recklinghausen when he studied spina bifida caused by improper fusion of embryonic tissues. Over the last century, its definition has widened to encompass split cord malformation (SCM), meningocele manqué, neurenteric cysts, dermal sinus tract (DST), lipomyelomeningocele (LMMC), fatty filum terminale, and tethered cord syndrome (TCS). Most of these disorders share their symptomology and clinical features. Most cause progressive neurological deficits, impairment, urological abnormalities, and orthopedic degradation to some degree, while some have no clinical symptoms [1].

The exact incidence of OSD is unknown, but with the dawn of technologically advanced imagining techniques such as computed tomography (CT) and magnetic resonance imaging (MRI), OSD lesions are becoming more and more readily identifiable and recognized incidentally.

Tethered Cord Syndrome

Tethered cord syndrome (TCS), filum terminale syndrome, or cord-traction syndrome denotes a gamut of congenital anomalies resulting in an uncharacteristically low-lying position of the conus medullaris [2]. The resultant sequelae are neurological sensory and motor deficiencies. TCS was first described by Fuchs in 1910 [3].

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He described urinary incontinence in patients with myelomeningocele when they flexed the spine and hypothesized that the incontinence was a result of abnormal spinal cord tension. Lichtenstein [1] added to Fuchs's hypothesis by describing patients with incomplete fusion and malformations, such as congenital abnormalities of the spinal cord and vertebral column, and linked spinal cord dysfunction and tethering lesions [1]. In 1953, Garceau invented the term "filum terminale syndrome." He observed three patients with progressive spinal deformity and neurological symptoms and deduced that this was due to a thickened filum terminale [4]. Not until 1976 was the term "tethered spinal cord" used by Dr. Hoffman and his colleagues. They described 31 patients who had elongated spinal cords with symptoms that improved after sectioning of the filum terminale [5].

Knowledge of the relevant anatomy and embryology is necessary to understand TCS fully. As described in a recent review by Lew and Kothbauer [6], the neural tube forms during neurulation at days 18–28 of gestation. The ectoderm that will eventually form the neural tube begins to close around days 22–23 and extends cephalad and caudad with the posterior neuropore closing by day 25–27. After neurulation is complete, the distal neural tube undergoes canalization and then neuralization. Undifferentiated cells from the primitive streak lead to formation of the caudal cell mass. This mass leads to the formation of vacuoles that fuse and develop into the distal neural tube. The caudal cell mass will in turn become the conus medullaris, filum terminale, and the cauda equina. By days 43–48, the ventriculus terminalis forms at the end of the neural tube near the coccyx, leading to the future location of the conus medullaris.

TCS has been studied extensively over the last decade, mostly in animal models. In a study of felines, Yamada et al. demonstrated that by adding weights to the filum terminale, simulating a tethered cord, they could identify the neurological effects of TCS. With tethering being greatest on the more caudal end of the spinal cord and the rostral end being more robust owing to the buffering ability of the dentate ligaments, blood flow and oxidative metabolism were significantly impaired. Using this model, the reversibility and the degree of injury were based on the duration and magnitude of the tethering. It was demonstrated that prolonged immobility of the spinal cord and nerve roots causes longitudinal stretching of the spinal cord, leading to blood supply compromise [7]. Koçak et al. conducted a study involving guinea pigs, using cyanoacrylate to fix the filum terminale [8]. They found that a simulated tethered cord caused ischemic injury and decreased conduction in motor and sensory nerve fibers. In previous studies, it was thought that the abnormal and inelastic filum can interfere with the embryological ascent of the conus medullaris relative to the vertebrae. This leads to a low-lying conus medullaris (below L1/L2), the characteristic trait of TCS. More recent studies have shown that over a 12-year period of tracking of 73 patients, 13 patients whose cord ended at or above the L1-L2 space still displayed symptoms of TCS [9].

In one case series by Khoshhal et al., 35 patients over 7 years were reviewed. The dysraphisms most frequently associated with TCS were lipomeningomyelocele (LMMC), found in 12 of the 35 patients (34.3%), myelomeningocele in 8 (22.8%), dermal sinus tract in 5 (14.3%), split cord malformation in 4 (11.4%), meningocele in 3 (8.6%), and a thick filum terminale in 3 (8.6%) [10].

OSD with isolated imperforate anus can be as high as 15% in TCS and patients with associated VACTERL as high as 60% [11]. Two of the primary and most prevalent associations with TCS are caudal agenesis and anorectal atresia syndromes. These include the OEIS cluster, imperforate anus, cloacal exstrophy, omphalocele, and spinal anomalies; VACTERL (vertebral anomalies, anal atresia, cardiac anomalies, tracheoesophageal fistula, renal and limb anomalies); and the triad of Currarino, anorectal malformation or congenital anorectal stenosis, sacrococcygeal osseous defect, and presacral mass. VACTERL is commonly associated with TCS and has been found in up to 78% of patients with a tethered cord [12]. TCS was associated with Currarino syndrome in up to 26.7% of patients [13, 14]. In another case report, ultrasonography revealed a sacrococcygeal teratoma associated with a tethered spinal cord during the 23rd week of pregnancy [15].

Miller-Dieker syndrome has been associated with TCS. TCS was secondary to a thickened filum terminale and/or a dermal sinus tract in two case studies [16, 17]. There has also been an association between Chiari type I malformations and TCS, one study showing that TCS was present with Chiari type I malformations in 14% of the patient population studied and 63% with low-lying cerebellar tonsils [18]. In another study of 170 patients with TCS, 10 (6%) had a Chiari type I malformation [19].

Fatty Filum Terminale

Fatty filum terminale is also known as lipoma of the filum terminale, thick filum terminale, or filar lipoma. The filum terminale is a fibrous band comprising two portions: the filum terminale internum, which connects the conus medullaris to the dural sac, and the filum terminale externum, which connects the dural sac to the coccyx [20]. A common cause of TCS, fatty filum terminale develops when the filum, which is normally a viscoelastic band that allows the conus medullaris to move slightly during spinal extension and flexion, is infiltrated with adipose tissue and becomes thickened. When there is excessive stress and traction caudally on the conus medullaris, the end result is a tethered cord [21]. Understanding the embryology of this condition, and other forms of TCS, is vital for understanding how such lesions occur: errors during secondary neurulation, when the distal spine caudal to S2 and the filum terminale form [22]. Errors during canalization or regression of the caudal cell mass between days 28 and 48 are believed to contribute to the formation of a low-lying conus, terminal lipomas, and fatty filum terminale [6]. McLendon et al. demonstrated that adipose tissue is a common finding in patients with TCS and can often be detected by computed tomography scans [21]. They suggest that adipose in the filum is not diagnostic for tethering of the spinal cord, but if the adipose is picked up by CT scans then the clinician should ask “is there tethering?” They also note that adipose tissue can be found in the filum terminale in about 19% of the asymptomatic adult population, while only 6% were detectable by CT. Tight filum terminale or fatty filum is said to constitute as many as 25% of all lesions causing TCS [22]. Interestingly, this common cause of TCS has been associated with pain

and with urinary dysfunction. Urological and neurological symptoms are a function of the magnitude and duration of traction placed on the spinal cord. Traction that has been sustained for a long time could potentially result in more severe and irreversible neurological dysfunction.

Finn et al. recently recommended that for symptomatic conus lipomas and filum lipomas, the treatment should be surgical intervention. If the patients are asymptomatic with a fatty filum, then close observation will suffice [23]. Most people consider surgical intervention appropriate for symptomatic patients with TCS and low-lying conus [24].

One study of 293 patients with TCS revealed that 190 (64.8%) had fatty filum terminale [25]. In another study of 33 patients with split cord malformations, 26 (78.8%) had a fatty filum terminale [26]. Approximately 67% of patients with syringomyelia have an associated fatty or tight filum terminale [27].

Neurocutaneous melanosis (NCM), where large congenital melanocytic nevi are associated with melanocytic deposits in the leptomeninges, has been identified in five cases over a 12-year period, all five patients having one or more spinal abnormalities. Three (60%) had a low-lying conus medullaris, of whom two had a fatty filum terminale causing a tethered cord [28].

Split Cord Malformation

Another major group considered part of the TCS spectrum is split cord malformation (SCM), diastematomyelia or diplomyelia (two hemicords). Diastematomyelia is a closed neural tube defect in which the spinal cord is longitudinally split by a fibrous band or a bone spicule. Split cord syndrome can refer to either diastematomyelia or diplomyelia. The nomenclature has been revised recently to eliminate some of the confusion in the literature. Diastematomyelia is a split cord in which the two halves are separated by a bone spicule and contained within separate dural sleeves; in diplomyelia the two hemicords lie within a common dural sac, more commonly with two complete sets of nerve roots, divided by a fibrous band [29]. In this section, we will use SCM and diastematomyelia interchangeably.

Diastematomyelia, found in a quarter of OSD patients, is thought to develop before primary neurulation or more specifically during gastrulation. Pang suggested that it arises during development when adhesions occur between the endoderm and the ectoderm, leading to the formation of a mesenchymal tract splitting the spinal cord [30]. The spinal cord is tethered at the level of the bisecting bony spur/dorsal band and/or by a fatty filum terminale. Clinical examination of these patients reveals cutaneous stigmata such as tufts of lumbosacral hair. About 85% of patients diagnosed with confirmed diastematomyelia demonstrated bony abnormalities, and 50% presented with scoliosis.

In previous studies [30], the symptoms of SCM were described as similar to those in TCS. Pang found that the adult SCM population he studied had severe pains in the legs and perineum with additional sensorimotor findings. Children presented slightly differently, with gait abnormalities but with less pain and progressive spinal

and foot deformities. Proctor and Scott (2001) found that while some patients with SCM presented with obvious urological symptoms, formal testing revealed occult urological abnormalities in as many as 75% [29]. Pérez et al. presented comparable results and recommendations. They studied 27 patients with SCM, 14 of whom had urological complaints, most commonly urge incontinence [31]. They suggest that all patients with confirmed SCM should undergo formal urological testing.

A characteristic of SCM is its unique tandem prevalence with other nervous system lesions, specifically fatty filum terminale, lipomyelomeningocele, myelomeningocele, and Chiari malformations. A recent study of 113 patients showed that 56 had one spinal cord lesion and 76 had two or more. One hundred and thirteen patients (100%) had a tight filum terminale, 26 (23.0%) a myelomeningocele, 23 (20.4%) a myelomeningocele manqué, 19 (16.8%) a meningocele, 12 (10.6%) an intradural lipoma, 8 (7.1%) a dermal sinus tract, 7 (6.2%) a hemimyelomeningocele, 6 (5.3%) an epidermoid, 5 (4.4%) a dermoid, 5 (4.4%) a lipomyelomeningocele, 5 (4.4%) an intrasacral meningocele, 4 (3.5%) a second SCM at a different vertebral level, and 1 (0.88%) a teratoma [32]. Another more recent study showed that 33 patients with diastematomyelia had a 78.8% likelihood of tandem thick filum terminale, 9.1% had dermal sinus tracts, and 6.1% a lipomyelomeningocele [26]. One source cites up to 38% of patients with SCM having simultaneous syringomyelia [27]. More recently, other studies have confirmed that upward of 50–85% of patients with SCM have a secondary comorbidity. Albright et al. mention that scoliosis in patients with a tethered cord and SCM is as high as 90% [27].

Lipomyelomeningocele

Lipomyelomeningocele (LMMC), or conus lipoma, a lipoma of the conus medullaris, is another key group of OSDs that leads to tethering of the spinal cord (TCS). LMMC results from an error during the first part of spinal cord formation, primary neurulation. Primary neurulation involves folding of the neuroectoderm and formation of the neural tube that becomes the spinal cord. This occurs on postovulatory day (POD) 18. The notochord induces the overlying ectoderm to proliferate as neuroectoderm, forming a groove that progressively elevates until it fuses and forms the neural tube. Superficial ectoderm separates from the neuroectoderm and fuses at the midline during disjunction. The mesoderm forms the posterior bony and soft tissue elements. Premature disjunction occurs when migration of the mesodermal elements that eventually form fatty tissue leads to a defect covered with skin or a closed defect due to ectodermal fusion preceding formation.

In previous studies it was noted that LMMC has a female to male ratio of 2:1 and an incidence rate of 1:400 [22]. Patients classically present with bladder dysfunction, intractable pain, cutaneous stigmata, and progressive neurological motor and sensory decline [33]. LMMCs are the most common type of spinal lipomas [23]. Commonly, investigation begins by noting cutaneous markers such as a subcutaneous lumbosacral mass, found in approximately 90% of patients. LMMC is commonly diagnosed during infancy [23, 34]. Other common stigmata are skin dimples,

hemangiomas, hair patches, skin tags, and depigmented regions. While cutaneous signs and neurological deficits are common, up to 48% of patients are completely asymptomatic and normal at presentation. As with other spinal dysraphisms, there is a strong neurological and urological deficit, the urological deficit being the most common initial neurological manifestation, seen in as many as 60% of patients with LMMC [35]. These patients have a progressive and downward deterioration of urological and neurological function. In one study, 62.5% of patients who presented at less than 6 months of age and 29% of those presenting at more than 6 months were asymptomatic [36]. In another study of 34 patients, all children above the age of 5 years were symptomatic, while all those under 4 years old were asymptomatic [37]. A large retrospective review on outcomes of patients with LMMC found that urological and bowel dysfunction did not improve over time. However, motor and sensory symptoms did show signs of recovery as 10 of the 11 patients undergoing surgical retethering went back to their preoperative functional status. Although asymptomatic patients are common, natural progression of the disease leads to neurological and urological deterioration, urinary bladder dysfunction typically occurring in the age range 0–2 years, while motor and sensory symptoms progress later in life, typically in the teenage and young adolescent years [38]. Early diagnosis, surgical intervention, and untethering are crucial for minimizing otherwise catastrophic neurological dysfunction [33].

As in other OSDs, the literature describes some peculiar yet interesting associations of LMMCs. TCS is fundamentally linked to LMMCs as the lipoma anchors the cord to the adjacent dura and soft tissue [39]. In a study of 97 patients, Hoffman et al. found a few common associations and noted that 4% had urological anomalies, 3.1% terminal hydromyelia, 3.1% dermal sinuses, 3.1% SCM, 3.1% dermoid and/or epidermoid cysts, 3.1% diastematomyelia, 1.0% anal stenosis, and 1.0% Down syndrome (trisomy 21) [36]. To compound these findings, Kanev et al. noticed a different set of anomalies in their patient set. Among 80 patients with confirmed LMMC observed over 35 years, 8.75% had scoliosis, 7.5% an amniotic band extremity deformity, 5.0% sacral dysgenesis, 2.5% hydromyelia, and 2.5% stenosis. More recently, Tubbs et al. noticed that Chiari type I malformation had a higher incidence in patients with LMMC than the general population. Among their 54 patients, roughly 13% with a Chiari malformation had a tandem LMMC [40]. Agopian et al. found 14.4% of their spina bifida patients to have LMMC [41, 42]. Currarino syndrome is often associated with LMMC, which is considered one part of the "triad of Currarino." The triad consists of an anorectal malformation (ARM), a sacral vertebral bony defect, and a presacral mass [14]. In 1 study of 13 patients with Currarino syndrome, 5 (38.4%) had LMMC [13]. To our knowledge, the literature describes two patients with LMMC together with duplication of the spine [43, 44]. The most common neural tube defects are encephalocele and myelomeningocele, and we discovered one case report of a patient who had a LMMC, complete situs inversus, occipital encephalocele, and tetralogy of Fallot. This was the first such case described and invites further research into links or associations between OSD and encephaloceles [45]. Among 11 patients identified with a collection of anomalies and lesions known as PELVIS syndrome (perineal hemangioma, external

genitalia malformations, LMMC, vesico-renal abnormalities, imperforate anus, and skin tag), 3 (27.3%) had a LMMC [46]. Sirenomelia or mermaid syndrome was found in one study in which all five patients with cloacal exstrophy had some form of OSD: four had terminal myelocystoceles and one had a LMMC [47]. Another case report identified a sacrococcygeal teratoma associated with a tethered spinal cord during the 23rd week of pregnancy by ultrasonography [15]. One study noted that up to 21% of patients with LMMC had associated syringomyelia [48]. Tubbs et al. found two patients with LMMC associated with Pacinian corpuscles [49].

Neurenteric Cysts of the Spine

First described by Puusepp in 1934, neurenteric (NE) cysts are erratic lesions of the central nervous system that are lined with intestinal epithelium [50]. The World Health Organization describes neurenteric cysts as "lined by mucin-secreting epithelium resembling that of the gastrointestinal tract" [51]. Spinal neurenteric cysts are congenital abnormalities derived from an anomalous connection between the primitive endoderm and ectoderm during the third week of life. The cysts are considered endodermal in origin because of such markers as vertebral anomalies, gut cysts, bowel reduplication, and keratin markers [52]. They have acquired numerous different names in the literature such as neurenteric cyst, enterogenous cyst, enteric cyst, gastrocytoma, dorsal enteric fistula, split notochord syndrome, and teratoid cyst [52]. Neurenteric cysts are not limited to the spinal column but can be found in other areas of the body, specifically the brain, mediastinum, abdominal cavity, and pelvis [53]. These alternative locations are rare, intraspinal neurenteric cysts accounting for 0.3–0.5% of all spinal "tumors" [54]. Neurenteric cysts are not true tumors in the traditional sense in that they do not arise from teratomas, but more closely resemble hamartomas, which are displaced pockets of endodermally derived tissue [49].

Neurenteric cysts can be located anywhere in the spine and present differently. Rauzzino et al. had 13 patients, ages ranging from 5 weeks to 52 years, most presenting early in life, classically during the first two decades, while older patients presented during their fourth decade. Presentation varied, younger patients presenting with the class of cutaneous markers associated with OSD, older ones with neurological dysfunction and pain. Their locations ranged from C2 to L5, with no lesions in the craniocervical junction. The cysts have most commonly been found in relation to the spinal cord, dorsal to the spinal cord as intradural and extramedullary masses and occasionally as an extradural dorsal mass. The second most common location for them is intramedullary, followed by anterolateral and anterior positions. Common locations along the vertebral column are thoracolumbar, upper thoracic, cervical spine, and lower lumbar region, in sequence from most common to least common [52].

Intraspinal neurenteric cysts can be stand-alone but have also been found with tandem congenital anomalies, 50% of presentations being accompanied by vertebral anomalies including vertebral defects, Klippel-Feil syndrome, spondylolisthesis and

other congenital defects such as meningomyelocele, syringomyelia, spinal lipoma, diastematomyelia, and intramedullary epidermoid cysts [55, 56]. Other simultaneous anomalies were mentioned in the study by Arai et al.; among their 43 cases with neurenteric cysts, two patients had grossly abnormal vertebral bodies, and two had myelomeningoceles [57]. Years later, Rauzzino and colleagues studied 13 patients and noted that 12 of them (92%) had a vertebral malformation in addition to the neurenteric cysts. Eight (62%) had posterior vertebral column abnormalities in the form of spina bifida, five (39%) had anterior vertebral column abnormalities, two (15%) had Klippel-Feil abnormalities, and two (15%) had scoliosis. They also noted that 69% of their patients had another form of spinal dysraphism, 31% having split cord malformations, 31% intradural lipoma, 23% fatty filum terminale, and 8% each having meningocele, meningocele manqué, and syringomyelia [52].

Compression of the spinal cord by neurenteric cysts and inflammatory reaction to the cysts' inner contents are the aggravators of most presenting symptoms [58]. Pain is the primary complaint, either radicular (31%) or local (54%), but there are other presentations, albeit rare, such as aseptic and bacterial meningitis, chronic pyrexia, and paraplegia [59, 60]. In some patients, symptoms have been reported to fluctuate, the two main hypotheses suggesting either the cyst itself ruptures or changes in the rates of mucin synthesis and reabsorption by the cyst wall [61, 62]. Classically, neurenteric cysts are insidious and even asymptomatic, so diagnosis is often delayed until the patients have suffered critical motor loss or other significant neuropathies [63].

Imaging modalities include plain spine roentgenograms, computed tomography (CT), and magnetic resonance imaging (MRI), the last named being the quintessential diagnostic modality [64].

Neurenteric cysts can easily be seen on MRI as hypointense on T1-weighted (T1WI) scans and hyperintense to isointense on T2WI scans compared to cerebrospinal fluid (CSF) [65]. The cystic fluid can appear hyperintense to isointense in comparison to CSF on both T1WI and T2WI owing to different protein content in the cyst fluid or to hemorrhage within the cyst itself. Rim enhancement is rarely achieved by contrast medium [65]. There are various surgical approaches, and one may choose one over the other depending on the location and level of the lesion [66–68].

Dermal Sinus Tracts of the Spine

Congenital dermal sinuses, a distinctive form of OSD that presents classically with meningitis, neural compression, and TCS, occur in about one in every 1500 births [69]. Dermal sinus tracts are lined with simple squamous epithelium and can penetrate anywhere in the midline from the occiput to the lumbosacral region [70]. The dermal sinus tract can traverse multiple spinal levels before it crosses the dural defect to an attachment on the spinal cord or filum terminale [71]. The etiology is thought to be failure during disjunction, causing adhesion between the neural and cutaneous ectoderm [72]. During embryological development the ectoderm

separates into two distinct portions, the neuroectoderm and the cutaneous ectoderm. This process, known as "disjunction," is thought to be the source of the error responsible for forming dermal sinus tracts, sometimes referred to as "incomplete disjunction." This abnormal disjunction, or failure to separate fully, takes place around the fourth week of development during primary neurulation. Gupta et al. found a correlation of 11.34% between dermal sinus tracts and other forms of spinal dysraphism [73]. Dermal sinus tracts can be associated with other abnormalities such as myelomeningocele, LMMC, and SCM [30]. Roughly 60% of dermal sinus tracts enter the subarachnoid space with up to 27% attached to the neural elements of the conus medullaris and filum terminale [74]. According Kanev and Park, the tracts can also end blindly within the extradural space in as many as 20% of patients and rarely end subcutaneously or within the paraspinal muscles [71].

Patients present classically with cutaneous stigmata such as a pit or dimple just superior to the intergluteal crease. Some patients also have skin tags, lipomas (subcutaneous), hairy patches or hypertrichosis, and hemangiomas. A rare finding, a pseudotail, a dermal appendage, has been reported recently in the literature associated with OSD, specifically alongside dermal sinus tracts [75]. The most common location for these stigmata is the lower lumbar or lumbosacral region, thoracic and cervical sinuses being significantly rarer [69]. Kanev and Park report an apparent male preponderance and infer that a family history of spinal dysraphism is highly unlikely. They state that all midline skin pits above the intergluteal fold should be assumed to communicate with intraspinal elements. Importantly, midline skin pits below the top of the intergluteal crease are blind to sacrococcygeal dimples, and there are no connections between the surface and intraspinal elements [71]. Dermal sinuses are dangerous because they can foster bacterial overgrowth and cause catastrophic infection, particularly meningitis and abscesses. They occur in approximately 50% of cases, the most common organisms being *Staphylococcus aureus* and *Escherichia coli*. Multiple episodes of meningitis and abscess can occur until the sinus tract is repaired [76].

Most patients have intact neurological functions at birth, but as they age and go through their growth spurts, symptoms begin to arise similar to those of other OSDs: pain, abnormal curvature of the spine, orthopedic deformities, gait disturbances, sensory and motor deficits, urological dysfunction, and weakness [77].

Ultrasonography easily identifies the subcutaneous tracts and also lesions associated with the dermal sinus tract, such as intraspinal inclusion tumors. Computed tomography using fine-section slices with sagittal reconstructions after administration of an intrathecal contrast agent is the method of choice for locating the bony landmarks and sinus tract attachment point. However, CT myelography is not recommended if a superficial sinus infection is suspected, as introducing the contrast agent can cause the organisms to spread to the CSF. Recently, CT studies have been replaced by high-resolution MRI, giving the provider a three-dimensional visualization of the tract path and other associated malformations. The sinus tract appears as a low-intensity tract that climbs into the subcutaneous tissue with high intensity on both T1- and T2-weighted images [78]. In contrast to the advantages of modern MRI, a normal MRI does not exclude the diagnosis of a sinus tract. Only about 40%

of dermal sinus tracts are detected by preoperative MRI, so if the MRI is normal and the tract is above the gluteal crease, surgical exploration is recommended [79].

Regardless of patient age or neurological pathology, dermal sinuses above the intergluteal crease should be surgically removed at the time of diagnosis to prevent future neurological sequelae and catastrophic infections [71]. Radmanesh et al. suggest that all dermal sinus tracts above the sacrococcygeal region should be explored operatively regardless of imaging [80]. A high index of suspicion is warranted for all dimples above the intergluteal fold regardless of imaging data. Any midline dimples need to be examined carefully when an infant suffers from meningitis caused by unusual organisms. Conservative treatment is contraindicated, and surgery should be carried out prophylactically on patients with advanced neurological deficits, to slow the advance of neurological compromise [81].

In 1 study of 33 patients, 3 (9.1%) with split cord malformations had a dermal sinus tract [26]. Dermal sinus tracts have been discussed in the literature. A case report identified 20 individuals with encephaloceles, a congenital malformation involving protrusion of the meninges and/or brain tissue, one of whom (5%) had a dermal sinus tract [82]. Radmanesh et al. described dermoid cysts as the neoplasms most commonly associated with dermal sinus tracts [83]. One study reported an association of 73% between dermal sinus tracts and dermoid inclusion cysts [80], though another study reported a lower association with a value of up to 50% [80].

Terminal Syringomyelia (Syrinx)

Syringomyelia is a fluid-filled cavity within the spinal cord and was first described by Ollivier d'Angers in 1827. Terminal syringomyelia, i.e., involving the distal third of the cord is a component of occult spinal dysraphism. Like many other OSDs, syringomyelia has been associated with myelomeningocele, LMMC, split cord malformation, Chiari type I/II malformations, and TCS. One review of 143 OSD cases over 20 years revealed that 24 (27%) of the 90 patients imaged with MRI had a terminal syrinx [84, 85]. Iskandar et al. found a 3:2 female to male ratio, the most common presenting symptoms of a terminal syrinx being scoliosis, back pain, bowel and urological dysfunction, and a multitude of neurological deficits.

The pathogenesis of syringohydromyelia is still contested, but many articles refer to the hydrodynamic hypothesis of Gardner and Goodall [86]. This is based on the premise that there are pressure differences between the brain and spinal canal. Gardner and Goodall propose that an obstruction in the fourth ventricle or at the level of the foramen magnum increases hydrostatic pressure and causes a shift of CSF from the brain to the central spinal canal. Other hypotheses propose a pathogenesis of syringomyelia secondary to arachnoiditis, trauma, and neoplasm. They suggest that ischemic changes in the spinal cord due to hypovolemia, arachnoiditis-induced

compartmentalization of the spinal canal, epidural venous congestion, and cystic degeneration of a neoplasm could all cause pressure differentials and shift CSF from areas of high to low pressure [85].

Classically, patients present with motor weakness, sensory and sphincter disturbances, and pain. There can be significant trunk weakness in some patients who have tandem scoliosis caused by the syrinx. Scoliosis and motor weakness are insidious in onset. In common with other OSD malformations, urological dysfunction is associated with syringomyelia. In the study by Iskandar et al., at least 16 (59%) of 27 patients with terminal syringohydromyelia had some form of scoliosis, and this is consistent with other studies showing a correlation between scoliosis and syringohydromyelia [87]. In the study by Iskandar et al., every patient had one or more tandem OSD malformations. Foot deformities, hypertrichosis, and capillary hemangiomas have been reported in other studies [88].

As with other OSD malformations, diagnosis is best made via high-resolution MRI with and without gadolinium enhancement. Gadolinium contrast agent allows for easy identification of the syrinx and demonstrates its magnitude and reveals any other OSD defects unknown to the provider [89].

Management can be difficult to navigate for this complex disorder. Anderson et al. followed 20 patients over 10 years without intervening surgically and found that about 35% showed no progression of symptoms, 55% had progressive symptoms, and 10% had showed intermittent progression after the initial presentation [90]. There are three broad categories of surgical treatment ultimately based around the differing hypotheses concerning the pathogenesis of syringomyelia. The first surgical approach is based on the Gardner and Goodall hydrodynamic hypothesis. The second group of operations is based on aspirating the cystic contents of the syrinx and the third category on lumboperitoneal shunting with the aim of lowering the craniospinal pressure gradients [37].

Terminal syringomyelia, like other OSDs, has common associations. The most common forms of OSD associated with syringomyelia are SCM, LMMC, myelomeningocele, and thickened filum terminale [91]. Syringomyelia is found in up to one third of OSD cases investigated by MRI scans [27]. Logue and Edwards studied 75 patients with syringomyelia and found that roughly 50% had scoliosis and a Chiari type I malformation [92], while another more recent study showed that 37 (13.5%) of 275 patients with syringomyelia had scoliosis [87]. Another recent study of 163 patients with syringomyelia showed that 59 (36%) had a low neck or hair line, 8 (4.9%) hydrocephalus, 1 (0.61%) Dandy-Walker syndrome, 54 (33.1%) kyphoscoliosis, 1 (0.61%) brain stem glioma, 4 (2.5%) a spinal cord tumor, and 4 (2.5%) an atlantoaxial dislocation [93]. The most common association with syringomyelia is the Chiari type I malformation, the hindbrain hernia. A study of 68 patients with Chiari type I malformation showed that up to 40% had syringomyelia between levels C4 and C6 [94]. Patients with myelomeningoceles had syringomyelia in up to 45% of cases [48, 95].

Conclusions

Many diagnoses may also have an associated form of the occult spinal dysraphisms. Each of these should be investigated in order to minimize long-term consequences of an untreated or unrecognized tethered spinal cord.

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Complications of the Occult Spinal Dysraphisms

19

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Although neurological deficits and complaints resulting from spinal dysraphism are frequently the most obvious result of tethered cord [1] and the most likely to be recognized by a neurosurgeon, patient quality of life often depends on the proper recognition and management of secondary effects outside of the usual boundaries of the nervous system. Patients with occult spinal dysraphisms may develop a variety of different complications as a result of the primary spine anomaly. These secondary complications are diverse and frequently require a multidisciplinary team of health-care professionals including orthopedic surgeons, urologists, and neurologists, neurosurgeons, physiatrists, physical and occupational therapists, and others in order to achieve the best possible outcomes for affected patients. Many patients with occult spinal dysraphism are diagnosed incidentally. Many of these patients will remain asymptomatic and may never require intervention. In general, lower conus position is associated with an increasing likelihood of symptomatic tethered spinal cord [2]. Patients with normal position conus are extremely unlikely to benefit from surgery. In this chapter, we outline the most common secondary complications of dysraphisms and describe the presentation, the treatment strategy, and, when known, the natural history for each of these conditions.

Cutaneous Associations of Spinal Dysraphism

Occult spinal dysraphism may present with characteristic cutaneous stigmata. The most well-known of these are the "faun tail" or hairy patch, a subcutaneous lipoma, hemangiomas, skin tags, nevi, and a dermal sinus tract [1, 3]. These lesions are found in many patients with occult spinal dysraphism and most commonly occur midline

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and in the lumbosacral coccygeal region [4–6]. The cutaneous lesions are often the initial finding that leads to a diagnosis of an underlying spinal abnormality [1, 3, 6].

Schropp et al. performed a prospective review of 358 children with occult spinal dysraphism to further characterize the associated cutaneous anomalies. They described 14 categories of cutaneous abnormalities, including subcutaneous lipoma, skin tag, deviation of the gluteal fold, coccygeal pit, atypical dimple (cranial to gluteal crease or outside the midline), porus/dermal sinus tract, skin dysplasia, a "cigarette burn" (scarred region), hemangioma, vascular nevus (not a true hemangioma), depigmented macula, hairy patch, hypertrichosis (more diffuse and less pronounced than the hairy patch), and meningocele [3]. In their study, 86.3% of patients had one or more cutaneous lesions. Subcutaneous lipoma was found most frequently, followed by vascular nevi and then sacral dimple, with 47.8%, 23.2%, and 10.6% incidence, respectively [3]. Zerah et al. divided cutaneous findings into three groups based on "risk" of finding an underlying spinal dysraphism. The "high risk" group includes subcutaneous lipoma, faun's tail, dermal sinus, or two or more of any cutaneous lesion. These patients had a strong association with underlying spinal dysraphism and [1]. The "low risk" group included patients with an atypical dimple, aplasia cutis, or deviation of the gluteal furrow [1]. The "very low risk" group included hemangioma, port-wine stain, hypertrichosis, fibroma pendulum, pigmentary nevus, and coccygeal dimple [1].

Some cutaneous lesions seem to correlate with particular underlying dysraphisms on observation studies. For example, a hairy patch correlates highly with split cord malformation [3, 7], while hemangiomas are often associated with simple fatty filum with tethered cord syndrome [6]. Although there is no proof of a causal relationship, or direct correlation, observation of any of the mentioned high risk category cutaneous lesions should initiate further imaging work-up in the proper clinical context.

Dermal sinus tract is the most important cutaneous manifestation of spinal dysraphism to recognize and treat. Failure to diagnose a dermal sinus tract may not only result in undiagnosed occult spinal dysraphism and therefore failure to prevent urologic, orthopedic, and neurologic decline but also may result in meningitis or even spinal abscess [1, 3, 8]. In general, when a dermal sinus tract is diagnosed, surgical evaluation is recommended to prevent meningitis and abscess [6].

Orthopedic Complications of Spinal Dysraphism

Common orthopedic complications of occult spinal dysraphism include scoliosis and kyphosis; foot deformities including cavovarus, pes cavus, and equinocavovarus; and unequal leg length [9]. These orthopedic abnormalities may result in gait instability, pain, and imbalance and are a significant contributor to patient morbidity [10]. In fact, one of the most common complaints and reasons for presentation with spinal lipoma or other occult spinal dysraphism is musculoskeletal issues, including back and leg pain or difficulty walking [9].

Scoliosis and kyphosis are common in occult spinal dysraphism, often with early onset and progressive decline, and correlate with motor and neurological level [10]. A

review of the causal relationship between tethered cord, syringomyelia, and scoliosis found level 4 evidence for association between lumbar lesions and curves less than 45° [9]. Multiple studies have been performed to evaluate the outcome in scoliosis after tethered cord release, with results showing that 50–100% of patients had progression of scoliosis after untethering, especially in patients with Cobb angles greater than 40° [11]. Scoliosis correction via segmented instrumental fusion is important for preventing progression of deformity and neurological decline [10]. Relative indications for fusion include Cobb angle greater than 50°, age greater than 10 years to preserve adult height, and progression despite conservative measures despite bracing [10], but surgical correction should be carefully considered using evidence-based medicine. It is probable that advances in our understanding in the pathophysiology of occult spinal dysraphism combined with improvement in spinal instrumentation techniques have resulted in increasing rates of diagnosis of secondary scoliosis and improvements in patient outcomes [10]. Additionally, while the degree of scoliosis correction is important and a critical component of scoliosis surgery, focus on additional outcome measures will continue to be a major focus for future outcome studies.

The proper evaluation and treatment of back pain can be challenging in the setting of both scoliosis and tethered cord. For properly selected patients with minimal scoliosis and a definitely tethered spinal cord, back pain has the best and most long-lasting response to tethered cord release surgery [11]. For these patients, lower extremity strength and gait, contractures, and spasticity improve in a significant majority [11]. Back pain that persists status post tethered cord release may be associated with scoliosis and will require an orthopedic evaluation.

Foot deformities are common in patients with occult tethered cord. In one large series, Gourineni et al. followed 151 pediatric patients with foot deformities and lipomeningocele over 8 years and recommended surgical correction in 122 patients, mostly in the first decade of life. The most common foot deformities seen in spina bifida include calcaneal deformity, cavovarus, equinocavovarus, cavus, and contractures [9, 10]. Surgical intervention for foot deformities, such as soft tissue release and osteotomy, may improve motion for patients with high-arched feet and claw toes [10]. When clubfoot deformity is causing substantial discomfort, talectomy and calcaneocuboid fusion should be considered [10]. While osteotomies are gaining popularity over arthrodesis for foot deformities [10, 12], arthrodesis without surgery is nevertheless a reasonable option and should be considered for the initial management of minor deformities. For these patients, long-term follow-up is strongly recommended to monitor for adjacent skin breakdown and adjacent joint arthritis [10, 13, 14]. Even when orthopedic surgical correction of a foot deformity is recommended, nonsurgical treatment such as physical therapy with muscle strengthening exercises, as well as orthotic devices, can clinically improve gait and function [10].

Urological Complications of Spinal Dysraphism

Urinary incontinence or other urologic dysfunction is a common manifestation of spinal cord tethering. For properly selected patients, early recognition and treatment with spinal cord untethering can result in most patients gaining continence [12,

15–17]. Importantly, however, since urological complaints are found in large numbers of even normal children, great care must be taken when selecting young patients for tethered cord release on the basis of urological symptoms alone.

The most common urological syndrome associated with symptomatic lipomas is sphincter disorders including micturition abnormalities such as incontinence, urge micturition, and retention [1, 2].

Children with frequent or recurrent urinary tract infections and pyelonephritis should be further evaluated for occult spinal dysraphism such as spinal lipoma, as this may be the only presenting sign of an underlying disorder [1]. Failure to diagnose occult spinal dysraphism and refer to neurosurgery may increase the risk of progressive urologic deficits and infections.

In asymptomatic patients with filum terminale lipoma, the risk of surgical complications outweighs the risk of conservative management, and there is never an indication for "prophylactic" tethered cord release for fatty filum alone [2]. Filum lipoma is sometimes detected as a finding of uncertain significance that comes to light in the course of an investigation of intractable urinary incontinence or chronic constipation. With the increasing use of MRI, fatty fila have been identified more frequently in asymptomatic individuals [18–20]. The clinical significance of a filum lipoma in an asymptomatic child is a subject of debate [19–21]. Division of a lipomatous filum for relief of tethering – a relatively simple neurosurgical procedure – is undertaken commonly for selected patients with pain, progressive neurological deficits, scoliosis, or disturbances of bowel and bladder function. Unfortunately, symptoms such as back pain and urologic complaints are common in children without neurological abnormalities, and many of these symptoms resolve with time, medical management, and behavioral therapy [22]. Therefore, the management of children with common urological symptoms is controversial in the absence of other findings, especially for those patients without lower than normal position of the spinal cord on imaging. Cools et al. reviewed a natural history analysis of 249 patients, including adults and children, with filum terminale lipoma over 3.5 years, with only 1 pediatric patient with new or worse symptoms [2]. When considering prophylactic surgery for incidentally discovered asymptomatic filum terminale lipoma, the risk of wound infections, meningitis, CSF leak, and pseudomeningocele must be carefully considered. We recommend conservative management for asymptomatic lipoma of the filum terminale.

Need for Lifelong Specialty Care

Patients with spinal dysraphism must be monitored carefully throughout their lives for signs or symptoms of secondary complications. Importantly, the need for comprehensive care and monitoring continues into adulthood since late deterioration is frequently noted, even after an excellent initial surgical outcome for the tethered cord [23, 24]. Late deterioration may be due to symptomatic re-tethering or the sometimes progressive natural history of the secondary disorders themselves [23]. A significant minority of patients will experience symptomatic

re-tethering after an excellent initial repair [9, 16]. Those with a fatty filum terminale are much less likely to recur following untethering compared with other types of tethered spinal cord [6, 16, 17]. Hoffman et al. proposed that adhesions and pathologic spinal cord fixation contribute to stretching of the cord, resulting in cord ischemia [25]. For symptomatic patients with recurrent tethered cord, surgical intervention is recommended, especially for patients who develop new or worsening deficits.

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Outcomes in Occult Spinal Dysraphism

20

Jeffrey P. Blount

Introduction

The comparison of outcomes between the natural history of untreated occult spinal dysraphism (OSD) and surgical results remains the central consideration in the clinical management of OSDs. There is general agreement that most forms of occult dysraphism have the potential to affect distal spinal cord function adversely and progressively lead to neurological, orthopedic, and urological decline (reviewed in Chap. 8 by Iskander and Amaefuna) [1–5]. However, different dysraphic conditions differ in the mechanisms by which they could plausibly cause harm, and there is likely to be more than one mechanism [6, 7].

For most OSDs, the natural history is sufficiently evident, and/or surgical treatment entails such modest risk that indications for surgery are clear [8–12]. For lipomas, there is more of a dilemma owing to the considerable variability in anatomy, presentation, and surgical outcomes of these lesions [7, 13–18]. There are multiple mechanisms of potential harm [6, 7]. As a result, lipomas are typically classified into symptomatic and asymptomatic lesions [15]. There is more or less universal agreement that symptomatic lipomas warrant surgical untethering, but the approach to asymptomatic lipomas is more varied [15, 18–24]. Pang and colleagues have for decades advocated radical excision and report unparalleled results [25–27]. A larger number of centers advocate subtotal maximum safe resection [4, 20, 21, 28–31], while others advocate a more conservative course, particularly in the asymptomatic child [6, 7, 32, 33]. Some centers started with aggressive optimal surgery approaches and evolved to a more conservative position when improvements from untethering did not persist [16]. There has been a recent effort toward

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defining a surgical candidacy classification that distinguishes patients by the type of dysraphism exhibited, chronological age, and symptom status [15].

There are many variables in precisely defining outcomes in OSD states. Some variables that can affect outcome pertain to the type of dysraphism, while others pertain to clinical considerations of the patient such as age and size. Outcome variables are varied and include multiple body systems such as neurological, urological, cutaneous, and orthopedic (joint and mobility) outcomes. In addition, there are symptomatic outcomes including pain and impaired sensation. No report comprehensively stratifies and correlates all of these variables. Some reports consider tethered spinal cord as a unifying clinical entity and combine the various tethering lesions, while others stratify by etiology or address outcome by symptoms or affected body system. Results have differed among centers and over time. Surgical technique, duration of follow-up, and outcome metrics are not standardized. This has contributed to the confusion and controversy surrounding management of the occult dysraphisms.

Overview: TSC as Final Common Pathway

An overview of occult dysraphism is best attained by considering outcomes from series that define tethered spinal cord (TSC) as the unifying event in the patient cohorts. These series typically focus on TSC as a final common pathophysiological pathway. Therefore, they inherently mix pathologies but also demonstrate the variations in surgical indication, technique, classification of pre- and postoperative results, and duration of follow-up. Most series either focus on adult patients or show heterogeneity in age with a predominance of older patients. Some reports combine occult dysraphism with TSC that occurs after closure of open myelomeningocele (MMC) or repeat untetherings. All entail a risk of selection and publication bias. It is therefore very difficult to compare outcomes directly or gain a sense of whether they are improving over time or with specific techniques. Despite these considerable limitations in study design and in the resulting literature, a number of recurring observations point to reasonable conclusions despite the insufficiency of formal supporting medical evidence.

Natural History:

1. The natural history of untreated symptomatic tethered cord syndrome is ominous. Regardless of specific etiology, multiple summary series of TSC have demonstrated a higher incidence of symptomatic progression of neurological deficit, pain, and sphincter disturbance for symptomatic patients who are either diagnosed late with TSC or observed rather than subjected to operative untethering [10, 34–38]. The most common symptom of TSC is pain, but various other symptoms can occur including LE weakness, numbness, and sphincter disturbance [28, 29]. Once neurological function is lost from symptomatic TSC, adults experience no functional improvement [15, 20, 34, 38–40]. Pediatric series demonstrate mixed results, but return of neurological function is rare [1, 11, 19, 20, 41]. Similarly, urological improvement is virtually never complete once lost,

regardless of treatment [23, 42–44]. Klekamp reported that the overall rate of clinical decline among nonsurgical patients was 20% at 10-year follow-up. The rate for symptomatic patients who were advised to undergo surgery but declined was 47% [45].

2. Most but not all patients harboring an OSD lesion develop symptoms. The most common symptoms are lower extremity dysfunction and pain [9, 11, 20, 23]. About a third have bladder or bowel dysfunction at presentation [15, 20, 24, 28]. When symptoms arise they are not specific to the type of lesion underlying the tethering. Rather, symptomatic patients with a range of dysraphic tethering lesions show similar complexes of symptoms. There is significant variability among the dysraphic lesions in respect of their propensity to induce symptoms. For example, nearly all split cord malformations and DSTs result in symptoms [46–48], but up to half of patients with conus lipomas remain asymptomatic [6, 7, 14]. Asymptomatic patients with conus lipomas remain the most difficult OSD patients to manage [15, 49, 50]. The percentage of patients with symptoms arising from filar lipomas appears to correlate inversely with conus position, but this remains very controversial [51–53]. Mixed cohorts demonstrate that patients with late symptoms following open MMC closure have symptom complexes similar to those harboring OSD lesions that have the potential to tether the cord [39–43].
3. The history of symptomatic TSC is progressive during the growth years of young childhood and adolescence but largely but not entirely stabilizes once growth ceases and the teen years and adulthood are reached [2, 27, 34–36]. Older patients with tethering lesions are more symptomatic than younger ones [24, 31, 39]. Recently, greater understanding of the broad spectrum of symptomatic OSD has increased awareness of the problem in adulthood and thereby increased the reported incidence of adult symptomatic OSD [12, 45, 54].
4. It is possible and even common for OSD lesions to exist in combination, and the clinical result will often reflect the effect of the most severe of these abnormalities [51, 52]. It is important to be alert to the possibility of simultaneous and complex lesions.

Surgical Treatment:

1. Pain is the preoperative symptom most responsive to relief by surgical untethering [12, 34–37, 39].
2. Long-term neurological stabilization is the most realistic attainable goal in patients undergoing untethering intervention for OSD. Expectation that lost neurological function will be restored is likely to be disappointed [15, 24, 33, 41].
3. Timing of intervention with regard to the evolution of symptoms is important. In multiple series, patients who underwent operative untethering when symptoms were minor or new reported better outcomes than those with advanced progression of symptoms [21, 24, 35, 41, 53, 55].
4. Urological improvement after surgical intervention is variable and virtually never complete. Children show more dynamic capacity for limited improvement in function than adults [23, 42–44, 56].

5. Surgical morbidity differs significantly among the types of OSD lesion, but surgical untethering entails low risk in most OSDs [8, 12, 35, 37]. Exact complication rates vary among combined series depending upon definitions of complications. CSF leaks, pseudomenigoceles, or hematomas occur in 5–20% of cases and wound infections in about 10% for most series [2, 4, 9, 10, 37, 55]. These complications are rarely threatening and can usually be managed with local wound care, reclosure, and occasional use of drains. Antibiotics are used if CSF leakage occurs. Permanent neurological deficit (PND) is the most serious complication of untethering surgery and depends mainly upon the type of OSD being treated. Filum lipomas have essentially no risk for PND, whereas complex or chaotic lipomas of the conus can be fraught with risk [6, 19, 31, 57, 58].
6. It is likely that the reported complication rates of PND are lower than those encountered in routine practice, owing to the effects of publication and referral biases.

Outcome by Tethering Lesion

Dermal Sinus Tracts (DST)

DST Natural History

The natural history of untreated DSTs is potentially highly dangerous. As detailed in Chap. 9, DSTs can become symptomatic and induce harm via infection (meningitis or focal/complex abscess) or by tethering [59]. The significant risk for devastating infection was recognized and publicized early in the twentieth century, so there has been no natural history study to quantify the rate of infection or tethering when DSTs are untreated [54, 60, 61]. Modern case series suggest that the most common presentation is a cutaneous anomaly and that infection is less common but can still occur [62–64]. Only 3/28 patients in the large series from Iowa had evidence of infection upon presentation. However, early case reports and small series demonstrate that the infections can be threatening enough to mandate treatment at first diagnosis.

DST Surgical Outcomes

Surgical outcomes in DST are excellent. Ackerman and Menezes observed that 82% of patients were either intact or improved following surgery, and no patient was neurologically worsened [62]. Radmanesh reported no neurological decline following surgical exploration and division of DSTs in a cohort of 34 patients [63]. Similarly, DeVloo and colleagues observed no serious surgical morbidity in a cohort of 14 cases operated on for DST over a 15-year period [65]. In the modern era, DSTs are detected because of cutaneous changes and are distinguished from more benign sacral pits on primarily clinical grounds [15]. Sacral pits lack associated cutaneous anomalies, and they reside within a normal gluteal cleft. Once confirmed, DSTs are promptly explored operatively and divided [64]. As emphasized in Chap. 9, surgical excision of DSTs is the standard of care and is associated with excellent outcomes if undertaken early in the life of the patient.

Split Cord Malformations

SCM Natural History

As detailed in Chap. 12, there are two forms of split cord malformation. Type I SCM have two hemi-cords in separate dural sleeves (formerly called diastematomyelia), while type II have a single sleeve with two hemi-cords that may be separated by a bony or cartilaginous spicule (formerly diplomyelia) [46, 52, 59]. Either form can be complex and heterogeneous, and the clinical variance can range from one minimal hemi-cord to highly complex anomalies [65–68]. There is a slight preponderance of females among patients who harbor SCMs (1.6:1) [46].

Other dysraphic conditions can occur in either of the hemi-cords, and others can appear in tandem (usually rostral) with the split [65, 67]. The natural history of untreated SCM has not been specifically studied, but many observations made on other tethering lesions apply. Many children with SCM are asymptomatic at birth and progressively develop severe neurological dysfunction as they age and grow [46, 52]. Children with SCM generally come to attention as a result of a cutaneous anomaly (focal hypertrichosis), whereas teens and young adults show progressive back, hip, buttock, and leg pain and demonstrate progressive neurological decline in the sphincters and lower extremities [48, 69]. In the large series from India reported by Mahapatra and Gupta, the two peak times of presentation corresponded to natural periods of accelerated growth [52]. The first was between 2 and 5 years and the second between 12 and 16 years. Another key observation from that report pertained to the modest rate of functional return once a deficit occurred. Only 39% of patients who presented with motor deficit and 27% with autonomic deficits showed any improvement [52]. Early prophylactic surgery is therefore widely recommended to avoid the kind of irreversible neurological insult that appears to increase with age and growth [52, 59, 70].

SCM Surgical Results

Because SCM is rare, only a few surgical series are available [51, 52, 67–71]. All are single-center, retrospective series and most are small. The largest series is from India, and the surgical objective was complete untethering, although symptomatic patients demonstrated consistent stabilization or improvement of motor, sensory, and continence functions [52]. Neurological status was preserved and remained static in 63% of patients who were symptomatic with progressive decline. Motor improvements were observed in 39% of patients, while 60% of those with sensory decline and 27% with incontinence demonstrated improvement with untethering. There was immediate postoperative neurological decline in 7% of patients, but this persisted in only 4%. Two thirds of the patients with neurological decline had SCMI anomalies [52].

Andar and colleagues studied 47 patients with SCM confined to the lumbar region [51]. They distinguished those demonstrating the “neuro-orthopedic syndrome” consisting of lower extremity asymmetry and modest-moderate sensory and motor dysfunction from those with progressive loss of function. They concluded that most SCM patients were in the former group, exhibiting fixed neurological

deficit with associated asymmetry and talipes, and surgery did not affect outcome. True, progressive dysfunction was less common but was not seen in any patient who had undergone prophylactic untethering. Other smaller series have demonstrated similar high rates of arrest of decline or improvement in neurological performance following untethering in SCMs. As a result, the surgical risk is thought to be less than the natural history of insidious neurological decline, and the presence of a SCM has evolved to fulfill the indication for operative untethering [51].

Lipomas

Filum Lipomas: Natural History

Lipomas of the filum (or filum terminale lipomas – FTL) are the most common spinal lipomas and are characterized by fat located entirely within the filum [72–75]. The filum is characteristically thickened, and histological examination demonstrates a mixture of fibrous tissue, elastin, and fat [51]. Cadaveric studies suggest that they occur in up to 5% of the population and MRI registries suggest an incidence rate of 1–4%. Increasing use of MRI imaging has led to more frequent discovery of these lesions, and controversy has arisen surrounding their role in occult tethered spinal cord.

A large comprehensive review of imaging and clinical records over a 14-year period at the University of Michigan correlated symptoms with radiographic findings for patients harboring FTLs; it revealed that over 95% of FTLs are asymptomatic [73]. The only factor that correlated with symptomatic presentation was a low (below L1) conus medullaris. However, most patients (73%) with a FTL and low conus were not symptomatic. Over a 3.5-year follow-up, only 1 of 249 patients with FTL demonstrated clinical decline. These findings suggest that a significant percentage of FTLs is asymptomatic even in the setting of low conus. There was also a difference between adults and children with regard to conus position; more children with FTLs were found to harbor a low conus [73]. These findings challenge widely held beliefs that filum lipomas cause TSC if the conus is in an abnormally low position and widely held practice preferences that they should be routinely ligated.

Filum Lipomas: Surgical Results

The thickened, fat-infiltrated filum of a filar lipoma has for many years been considered a primary source for tethered cord syndrome [74–76]. The concept that traction induces impairment of function and that symptomatic patients with filar lipomas and low conus ought to undergo filum clipping is widely accepted among pediatric neurosurgeons [52, 72, 77]. More than 90% of the participants in a 2005 practice survey of pediatric neurosurgeons said they would clip a filar lipoma associated with low back pain and urodynamically verified neurogenic urinary incontinence [78].

Multiple single-center, retrospective case series of filum lysis have demonstrated clinical stabilization or improvement of pain and neurogenic (urodynamically verified) urinary incontinence in 70–90% of patients and very few (<2%) operative complications [30, 52, 56, 58, 79–81]. Selden reviewed the English language

pediatric literature about filum section between 1964 and 2005 [77], identifying five retrospective observational, non-controlled studies of filum section in patients (n = 161) already medically optimized for voiding dysfunction. The overall rate of improvement following section of the fatty filum in setting was 87%, and the incidence of complications was 1.9%. Unfortunately, the methods in each of these studies entailed significant potential for bias, and the imperfections in study design meant that the quality of evidence was modest [77].

The controversy has been extended with the proposal that tethered cord syndrome can occur when the conus is in a normal position [56, 81–83]. The first paper to report this phenomenon was by Khoury et al. who in 1990 reported a cohort of patients with abnormal voiding, abnormal urodynamics consistent with tethered cord, osseous spina bifida, and a normal position conus [56]. When the fila were sectioned, 70% of patients demonstrated improved volitional bladder control [56]. Shortly thereafter, Warder and Oakes presented a cohort of 13 similar patients, among whom 75% with voiding difficulty improved [82]. A subsequent series of small retrospective observational cohorts has demonstrated improvements in most of the variably selected patients undergoing lysis of filar lipomas with conus in the normal position [77, 84, 85]. Broad approval of this approach has been reserved owing to the seeming lack of standardization of candidacy by symptoms or radiographic findings, unifying physiological principles, or external observer validation, and other design flaws in these reports. Nevertheless, appropriate treatment of filar lipomas with the conus in the normal position remains an active and vigorous area of controversy.

Conus Lipoma: Natural History

Lipomas of the conus occupy the center of the controversy surrounding lipoma management. Few areas of surgery offer such a broad range of approaches advocated by experienced surgeons. Conus lipomas are highly heterogeneous in form and presentation but have been classified by two widely used systems. Chapman defined dorsal, terminal, and transitional forms of conus lipoma on the basis of the predominant direction in which the fatty, fibrous mass projects from the conus. Inherent in this classification system is a hierarchy of surgical complexity that reflects increasing anatomical complexity and interdigitation between the fibro-fatty tissue of the lipoma and the conus or exiting nerve roots [74, 86]. Pang's system of classification includes dorsal, transitional, and chaotic forms, which progressively and sequentially reflect greater complexity associated with greater surgical challenge and risk [25]. These lipomas are discussed in further detail in Chap. 11.

The central observation related to the natural history of conus lipomas is that the neurological, neuro-urological, and neuro-orthopedic deficits that accompany them increase over time [15, 21, 29, 30, 74, 86–88]. Adults and teens present with more deficits and symptoms than babies and young children. Patients who have been (historically) observed over time without intervention tend to progress in the extent and severity of their symptoms and deficits [21, 30, 31, 53, 86]. The observed progression led to the conclusion that progressive tether over a young lifetime of growth was the exclusive or predominant pathophysiological mechanism by which

deficit was increased [89]. Surgical intervention to disconnect the lipoma from the surrounding soft tissue could presumably interrupt the inexorable decline associated with tethering [89]. This concept energized an initial surgical enthusiasm and a widely held management strategy that conus lipomas should be operated upon to disrupt this preventable decline [20, 21, 39, 88, 90]. Over time, this initial enthusiasm became tempered when long-term follow-up from multiple surgical series demonstrated recurrences of symptoms in significant percentages of patients who underwent untethering surgery [14, 18, 32, 33, 91, 92]. Goodrich and colleagues performed a meta-analysis of 608 patients who underwent untethering for tethered cord and found a linear relationship between the duration of postoperative follow-up and the incidence of re-tethering symptoms [22]. The early enthusiasm for aggressive surgery was further tempered by a growing awareness of complications and the observation that the natural history of conus lipomas was more variable and in many cases less threatening than initially thought [6, 7, 19, 33, 50].

Several experienced surgical groups challenged the concept that the natural history of all untreated lipomas was uniform progressive neurological decline. Kulkharni and colleagues followed a cohort of asymptomatic patients with lipomas prospectively, watching for any signs of neurological progression [7]. They observed only a 33% incidence of neurological decline. The neurosurgical group at Great Ormond Street Hospital similarly followed a prospective cohort and observed a 6% rate of neurological decline [3]. Each group that has challenged the exclusive role for tether in imparting deficit in conus lipomas has emphasized other possible contributors to the pathophysiology. First among these are fundamental defects in secondary neurulation that cause primary, fundamental impairment of function [6, 7, 14]. Conus lipomas are highly complex congenital anomalies with extraordinary anatomical variability and are likely to harbor neurological dysfunction irrespective of tether. Another important contributor to symptom evolution is the natural maturation and growth of the child. The deficit can be hidden in young children owing to inherent difficulties in discerning nuances of capability. Refined capabilities of urinary continence or sexual function only become evident after the young childhood period [6, 14]. Older children and young adults are also larger and can suffer pain from greater weight on inherently malformed spines and lower extremities [14].

In practical terms, there was regionalization in the interpretation and understanding of the natural history of conus lipomas. The centers that challenged tether as the sole pathophysiological mechanism were initially European and subsequently Canadian, while American and Asian centers vigorously embraced the centrality of tethered cord in the natural history of conus lipomas. The vigor with which influentially dominant centers embraced tether made studies of natural history challenging as failure to intervene in the face of threatened decline was considered neglectful of the patient's need [20, 39]. At present, the predominant view appears to be awareness of variability against a predominant backdrop of progressive decline of function. Coupled with the observation of modest surgical outcomes for lipomas, this has opened the reasonable option of observing patients with conus lipomas until symptoms first emerge and then untethering. Whether such delays impair physiological reserve and make surgery less effective or safe is still speculative and uncertain but remains at the cornerstone of the surgical challenges of conus lipomas.

Conus Lipomas: Surgical Results

Surgical treatment for conus lipomas initially followed treatment advances for open MMC. About 35–40% of patients undergoing closure of MMC in infancy develop pain and neurological decline in the lower extremities and sphincters that responds favorably to surgical exploration and untethering [39]. The similarity of the clinical phenomenon between occult and open dysraphic patients promoted the initial insight and surgical rationale for untethering in conus lipomas. Most early results were favorable, and many clinical series have combined patients with different forms of dysraphism. Herman and McLone documented 75% improvement in pain and 65% arrest of neurological decline with a less than 10% rate of complications [39]. Byrne demonstrated near-uniform rates of stabilization or improvement [3]. Many retrospective, single institution surgical series in conus lipomas have shown favorable outcomes (stabilization of decline and improvement of pain) with low surgical risks [19, 20, 24, 41, 49, 50, 53, 86–88]. However, these studies were methodologically flawed, had nearly exclusively short-term follow-up, and were subject to observer and selection bias. Greater experience led to the observation that a significant percentage of patients who underwent untethering for conus lipomas showed continued or recurrent late neurological deterioration, which was presumed to be due to re-tethering [4, 16]. Coupled with observations about more variable inherent rates of neurological decline with conus lipomas, this provided the rational basis for the evolution of a more conservative initial approach at some centers [6, 7, 16]. Perhaps the clearest example occurred in the findings by the group in Paris [16]. Initially, all children harboring a conus lipoma underwent uniform prophylactic untethering. However, over time, 60% of the patients who were untethered showed late progression of neurological decline [16]. This prompted a clinical evolution toward observation until the emergence of symptoms in their paradigm for conus lipoma management. Subsequent studies in North America have yielded a wide range of actuarial risks (20–70%) for progressive neurological decline despite prophylactic surgery for conus lipomas [6, 14, 18, 22].

Talamonti and colleagues prospectively followed a cohort of pediatric patients with asymptomatic conus lipomas, whose families were offered either observation or prophylactic untethering [49]. Symptomatic tethered cord occurred in 10% of those who underwent surgery and 29% who were observed, but the small size of the cohort limited the power of the study [49].

Pang also reviewed his initial experience with conus lipomas and found dissatisfaction with outcomes because of recurrence when untethering was done using conventional limited resection techniques. In response, he returned to the laboratory, studied the embryology comprehensively, developed a new classification for conus lipomas, and developed a new radical surgical approach that completely revamped previous surgical paradigms [65, 67]. Radical resection techniques and variables are detailed in the chapter on lipomyelomeningoceles, but they have generated progression-free survival rates of 82% at 16 years for all types of conus lipoma. Previously unoperated cases showed 98% progression-free survival in Pang's ongoing longitudinal analysis, which now exceeds 15 years [26]. The challenge to this approach lies in how widespread is its applicability and utility. Despite a significant

number of fellows and students, there have been relatively few reports from other centers to validate the usefulness and applicability of these techniques.

Currently, therefore, there are three broad surgical paradigm approaches to conus lipoma. The conservative group holds that natural history is variable, that not every patient will decline, that symptomatic recurrence is common after surgery, and that surgical risks are significant. Observation of patients with serial examinations and intervention for demonstrated decline is therefore the preferred paradigm. The conventional "maximum safe resection" group advocates prophylactic intervention before symptoms but limits the resection to the maximum that can be obtained without causing neurological injury. This group appears to be the largest and to reflect conventional beliefs and biases concerning conus lipomas. The radical resection group espoused by Pang advocates specific surgical techniques dictated by consistent findings in the pathological anatomy and strives for complete resection of the lipoma. Despite its conceptual appeal for many surgeons, the techniques are demanding to the point of grueling and remain elusive for most surgical groups. Only limited numbers of reports beyond Pang's own large longitudinal series support this approach.

Conclusions

Neurological decline typically accompanies growth and age if there is a dysraphic tethering spinal lesion. This central observation has given rise to the concept of tethered cord syndrome and shaped the approach to occult dysraphism over the past generation. Untethering procedures are performed to divide the connection between the spinal cord and the tethering dysraphic lesion surgically, thereby disrupting the pathophysiological cycle. In the real world, the rational basis for any such intervention carefully maintains a constant comparison between the natural history of the untreated lesion and the surgical risks involved in untethering.

Ultimately, the appropriate approach for a given surgeon or team arises from consideration of the natural history of the lesion compared with their individual surgical results. For this reason, it is crucial that serious surgical students of spinal lipomas continuously evaluate and tirelessly and meticulously strive to optimize their techniques, optimize technological adjuncts such as intraoperative monitoring, monitor their outcomes, and adjust their practices on the basis of this important balance.

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Genetics and Developmental Biology of Closed Dysraphic Conditions

21

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Introduction

Closed spinal dysraphism comprises a number of diverse pathologies with varying morphology and severity, which can be isolated or associated with anomalies in other body systems. The term 'spinal dysraphism' is generally understood to mean 'congenital abnormalities of the vertebrae and spinal cord or nerve roots'. On the other hand, the basis of the word dysraphism – 'raphe' – is strictly 'a groove, ridge or seam in an organ or tissue, typically marking the line where two halves fused in the embryo'. Hence, spinal dysraphism actually refers to midline fusion defects. Appending the word 'closed' effectively rules out almost all neural tube fusion defects which generally involve open not skin-covered lesions (e.g. myelomeningocele); hence spinal dysraphism in its current usage is actually a misnomer. In this chapter, we consider the genetics and developmental biology of a range of skin-covered malformations of the low spine and/or nerve roots and their associated vertebral anomalies.

Traditionally, the rare and often complex spinal dysraphic pathologies have prompted intense speculation on possible pathogenic mechanisms. The starting point for such speculation is usually the anatomical appearance of affected foetuses or more often postnatal individuals, at the time of diagnosis, surgery or even death. A process of 'backward extrapolation' is then carried out, to deduce the embryonic and foetal events that are surmised to underlie the pathology. While such an approach is a useful hypothesis-generating exercise, it has rarely been followed by experimental testing. In consequence, paediatric neurosurgery and related fields suffer from a plethora of untested and largely unsubstantiated hypotheses regarding the pathogenic mechanisms underlying low spinal malformations.

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As an alternative approach, in this chapter we summarise the genetics and developmental biology of low spine formation, based on research in animal models, and ask to what extent these principles of normal development may apply in interpreting human pathology. We draw attention to the extreme paucity of definitive information on the genetic basis of closed spinal dysraphism. In a few cases, animal models have proven useful and may suggest possible causative factors (mainly genetic) and pathogenic mechanisms that may underlie the origin of closed spinal dysraphism in humans.

Approaches to the Genetic Analysis of Congenital Disease, Including Spinal Dysraphism

The genomics revolution of the last 25 years has enormously impacted research into congenital disorders [1]. First, it has provided tools to perform an unbiased search through the genetic material of affected individuals, for example, by whole genome or exome sequencing, and then to evaluate candidate gene variants for disease association and possible causation. A second innovation has been the development and analysis of animal models of human spinal disorders where the genetic causation, and sometimes the pathogenic sequence of events, can be experimentally identified. In the following sections, we review the main features of these patient-oriented and animal model-based approaches and then consider the extent to which they have impacted our understanding of the causation and pathogenesis of closed spinal dysraphism.

Patient-Oriented Genomic Approaches

High-throughput DNA sequencing is an increasingly popular, unbiased approach to identify genetic variants as candidates for disease causation. The strategy requires only small numbers of cases, which makes it particularly attractive for conditions like closed spinal dysraphism, where relatively few patients are usually available. Ideally, the analysis is performed in a family of affected and unaffected individuals, but it can also be undertaken in a group of unrelated (sporadic) cases, provided the phenotype (and, hence, presumed causation) is relatively homogeneous. Either the coding regions of all genes are sequenced, to generate the ‘exome’, or the entire coding and non-coding genome is sequenced. Thousands of variations from the ‘standard reference’ human exome or genome sequence are identified and these need to be filtered sequentially to remove likely non-significant variants, e.g. harmless polymorphisms. The aim is to generate a manageable list of potential candidate genes that harbour a potentially damaging ‘mutation’ in cases but not in unaffected controls. Candidate genes are often ranked in priority at this stage, based on their known involvement in cellular functions that might suggest a role in disease causation.

Genome-wide association study (GWAS) is an alternative unbiased approach to disease gene identification, which seeks 'associations' between candidate loci and disease. Single nucleotide polymorphisms (SNPs) are highly abundant genomic variants that can serve as 'tags' for particular genes. The method assesses whether disease occurrence is in 'linkage disequilibrium' with candidate gene SNPs: i.e. non-random associations suggest genetic linkage. In GWAS, the method evaluates association with SNPs mapping across the genome. However, large numbers of affected individuals are needed for this approach and GWAS studies are difficult to apply to relatively rare conditions such as closed spinal dysraphism.

Establishing causation for a gene variant is often very challenging, especially when a variant exists only in a single family or in a few sporadic cases. Software (e.g. SIFT or PolyPhen-2) can analyse sequence data and predict which variants are 'damaging' or 'benign', but this is not an infallible approach: mutations with known functional effects are sometimes labelled 'benign' by such software, and vice versa. Expressing the mutant and wild-type proteins in cultured cells, to study effects on in vitro function, is a useful test of effect [2] but can only give clues to disease causality. In a few cases, direct comparison of mutant and wild-type protein function has been possible, e.g. where the gene product is an enzyme [3]. Probably the most powerful approach is to introduce the putative mutation into an animal model to determine whether a similar phenotype is produced as in human. The advent of CRISPR/Cas9 technology for rapid gene editing [4] should make such functional studies in both cells and animal models more feasible in the future.

Insights from Mouse Genetic Models

Animal models offer an opportunity to conduct experimental studies to reveal pathogenic mechanisms of congenital disorders. Such studies are not possible in humans where only descriptive analysis can be undertaken. Hence, the analysis of animal models is usually an essential part of the journey towards an in-depth understanding of a disease process. However, a number of factors may limit the value of animal models for understanding human pathogenesis. Many models are in lower vertebrates (e.g. birds, amphibia or fish) or even invertebrates (e.g. the fruit fly *Drosophila* or the nematode *Caenorhabditis*), and, although such models offer valuable insights into general mechanisms, our ability to extrapolate directly to humans is limited. In contrast, the mouse as a mammal has much greater extrapolation potential and, importantly, has excellent genetic tools that enable experimental analysis of disease mechanisms.

The International Mouse Phenotyping Consortium (IMPC; www.mousephenotype.org/) aims to 'produce and phenotype knockout mouse lines for 20,000 genes', i.e. for most of the genes in the genome. Several thousands of genes have already been inactivated in mice, through gene targeting technology [5], and a wealth of developmental and other phenotypes has been identified. For example, more than 200 different genes yield open neural tube defects (NTDs) when individually

inactivated in mice [6, 7], attesting to the genetic complexity of neural tube closure. A range of phenotypes is observed, with the majority of mutants exhibiting exencephaly (the developmental forerunner of anencephaly) and a smaller number yielding open spina bifida (i.e. myelomeningocele), often with tail flexion defects. While such single-gene, loss-of-function models are invaluable, it should be noted that human developmental disorders can arise from increased gene expression, which is not routinely modelled in mice, and that gene-gene or gene-environment interactions are also likely to be of critical importance. Such interactions can be modelled in mice, but this requires a knowledge of likely candidate genes for the condition.

A limitation of mouse models of congenital disease is the marked difference in gestational length from human. The mouse is born at a relatively immature stage, and while it may efficiently model early-arising human defects, those that develop at later embryonic and foetal stages (which may be the case with some forms of closed spinal dysraphism) are likely to be less well reproduced. There is also a paucity of mouse models for certain disease entities, including closed spinal dysraphism. This contrasts with open NTDs where there are many models and probably reflects the relatively 'subtle' external appearance of skin-covered spinal developmental lesions compared with open NTDs. Even if a closed spinal defect is present in a newly created knockout line, it may go unnoticed during the initial characterisation of the mutant line.

Developmental Biology Events Relevant to Low Spinal Development: An Overview

In this section, we review some of the main events of embryonic development, considering which are likely to have direct relevance to the pathogenesis of conditions classified as 'closed spinal dysraphism'.

Gastrulation This process converts the bilaminar embryo into a trilaminar structure, generating the three definitive germ layers and specifying rostro-caudal and left-right body axes. Mesoderm and endoderm are generated when cells of the pre-gastrulation epiblast layer pass through the primitive streak and node, respectively, while ectoderm arises from epiblast that remains on the dorsal surface. At first sight, gastrulation might be considered a prime candidate for disruption leading to congenital spinal defects, as cells with ectodermal, mesodermal and endodermal characteristics often coexist in a disorganised fashion in dysraphic states. However, in recent years it was demonstrated that gastrulation generates tissues only at cranial and cervical levels of the body axis, as far caudally as the sixth somite [8]. More caudal levels arise from progenitor cells in the 'tail bud' region (also called the caudal eminence or end-bud). Hence, the gastrulation process itself is unlikely to be implicated in the origin of closed spinal dysraphism.

Neuro-mesodermal Progenitors (NMPs) The existence of self-renewing progenitor cells in the caudal embryonic region (Fig. 21.1) was originally inferred from clonal analysis in mice: cells of both neurectodermal and mesodermal types were found to arise as the mitotic descendants of single tail bud cells [9]. As endoderm was rarely observed among these descendants, the parent cells were named 'neuro-mesodermal progenitors', but they might have broader potential. Such cells are thought to be defined by co-expression of the transcription factors Brachyury and Sox2, which play master regulatory roles in the subsequent development of mesoderm and neurectoderm, respectively [10]. Moreover, it has proven possible to generate cells resembling NMPs from embryonic stem (ES) cells, of both mouse and human origin, by treatment in vitro with specific 'differentiation protocols'. For example, fibroblast growth factor (FGF) and Wnt exposure are essential to generate cells with

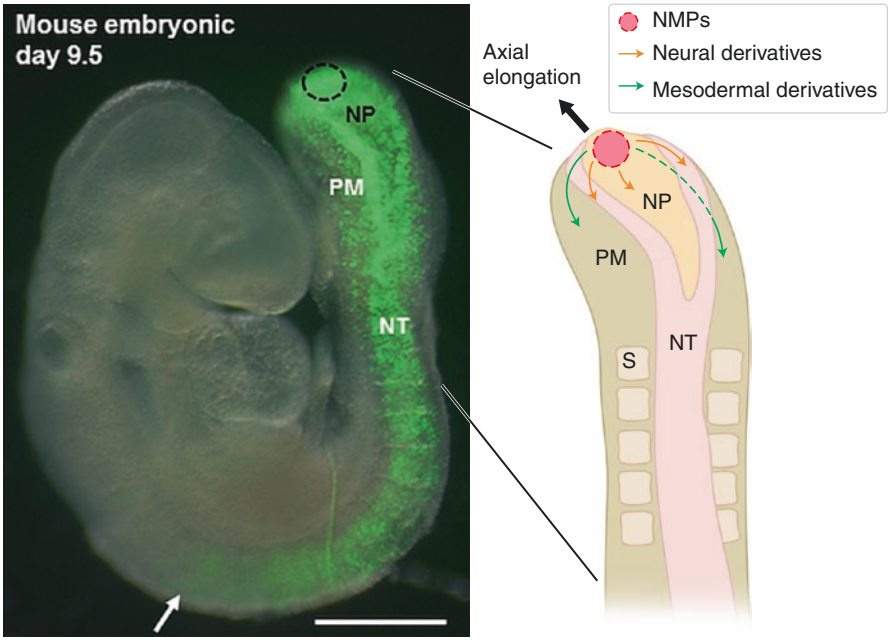

Fig. 21.1 Neuro-mesodermal progenitors (NMPs) in mouse embryonic development. Transgenic mouse embryo of genotype *Nkx1.2*^{ERT2Cre}; *ROSA26*^{YFP}, 24 h after maternal intraperitoneal injection with tamoxifen (left). *Nkx1.2* is expressed in NMPs, and so tamoxifen induces Cre-mediated recombination of the floxed YFP sequence, generating green fluorescence expression in NMPs and their mitotic descendants. The strongest YFP expression is in the tail bud (dashed circle) where the self-renewing NMPs are located. Both open neural plate (NP) and closed neural tube (NT) are also strongly YFP-positive, reflecting neural contribution of NMP descendants. Paraxial mesoderm (PM) is YFP-positive, albeit less intensely, consistent with the multipotent nature of the NMPs. Note that YFP expression has a rostral boundary in the upper spinal region (arrow) indicating the transition level from gastrulation-derived to NMP-derived body axial tissues. Diagrammatic representation of the caudal spinal region (right) indicates the dual function of the NMPs: to mediate axial elongation while also supplying cells to both neural and mesodermal lineages. *S* somite. Scale bar: 0.5 mm

NMP potential. Mesoderm differentiation can then be induced by continued exposure to Wnt, while neural differentiation is induced by exposure to retinoic acid plus stimulation of sonic hedgehog (Shh) signalling [11]. Hence, bi- or multipotential cells exist within the caudal embryonic region and these are strategically placed to participate in the generation of low spinal dysraphic conditions.

Convergent Extension (CE) This embryonic shaping process recently came to prominence as a vital event for initiation of neural tube closure. During and following gastrulation, cells in both neurectoderm and underlying mesoderm alter their positions, causing a net lateral-to-medial displacement of cells in the plane of the tissues. Cells intercalate in the midline causing the body axis to narrow and simultaneously elongate rostro-caudally. CE cell movements require planar cell polarity (PCP) signalling, a non-canonical Wnt/frizzled/dishevelled pathway that regulates cytoskeletal function and hence cell shape and motility [12]. If CE is compromised through mutation of PCP genes, embryos develop an abnormally short, broad neural plate that fails to initiate neural tube closure, yielding the severe open NTD craniorachischisis [13]. There is also increasing evidence that CE plays a role in shaping the developing neural tube at later developmental stages and hence could be involved in the pathogenesis of dysraphic conditions in the low spine.

Primary and Secondary Neurulation The embryonic neural tube is the development precursor of the entire brain and spinal cord, and so its development is expected to be pivotal in an understanding of spinal malformations. In terms of embryonic morphogenesis, neurulation begins with folding and fusion of the neural plate, so-called 'primary' neurulation, which initiates at the hindbrain-spinal cord boundary and then spreads throughout the brain and gradually along the spinal region. Progressively lower levels of the spinal cord are formed as closure, which resembles the travel of a zip fastener, gradually passes down the body [14]. At low spinal levels (upper sacral region), primary neurulation is completed and neural tube formation transitions to a different process, 'secondary' neurulation, in which the emerging neural tube is internal, covered by future epidermis, throughout its development (Fig. 21.2). The secondary neural tube forms through a process of dorsal midline aggregation of mesenchymal tail bud cells, followed by 'canalisation' in which the cells adopt an epithelial morphology, arranging themselves around a lumen to form the secondary neural tube [15]. Hence, defects of primary neurulation yield open NTDs, as confirmed by studies of mouse embryos, whereas secondary neurulation disorders are associated with skin-covered defects, as exemplified by closed spinal dysraphism.

Neural Crest (NC) In the spinal region, this population of cells separates from the dorsal part of the recently closed neural tube and migrates along specific routes to contribute to neural and non-neural tissues [16]. Sensory and sympathetic ganglia are formed by NC, as are all the melanocytes of the skin. Hence, differentiation of NC cells has the potential to generate a variety of tissue types and, if the cells became misrouted and/or altered in differentiation, they could be involved in

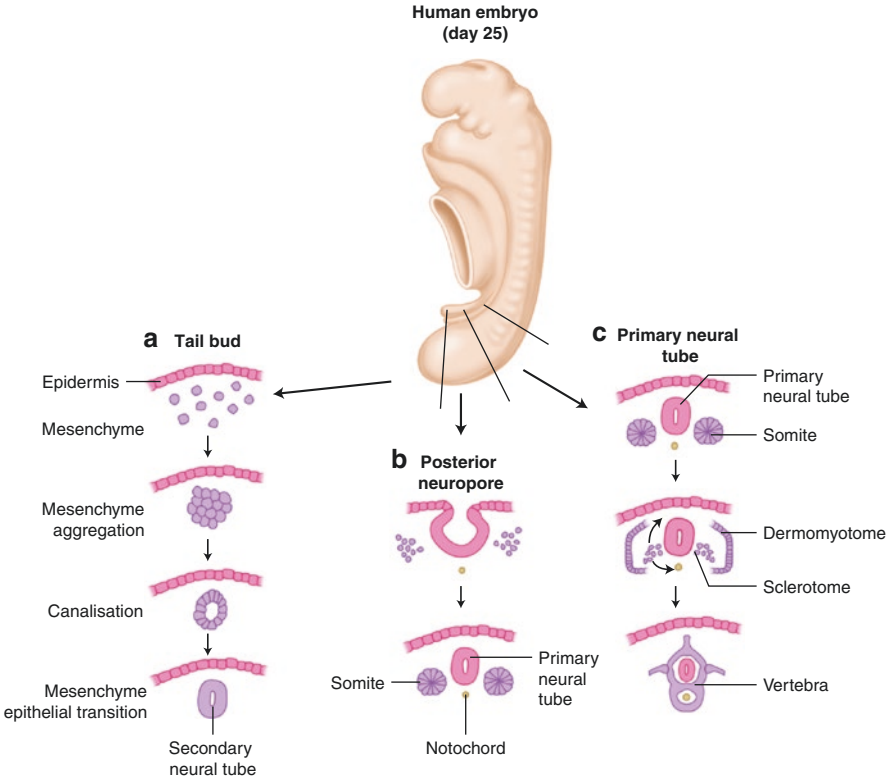

Fig. 21.2 Diagrammatic representation of key events in low spinal development. Schematic transverse sections at three low spinal levels, as indicated by the lines on the embryo diagram. Developmental events are depicted from early to late stage in each top-to-bottom sequence. (**a**) Sections through the embryonic tail bud show future epidermis (non-neural ectoderm) overlying tail bud mesenchyme. Mesenchyme sequentially undergoes aggregation (condensation), canalisation and mesenchyme-epithelial transition to form the secondary neural tube. (**b**) At posterior neuropore level, the neural plate folds and fuses dorsally, creating the primary neural tube. Presomitic mesoderm flanking the closing neural tube undergoes mesenchyme-epithelial transition to form somites soon after closure is complete. (**c**) At the level of closed primary neural tube, somites subsequently differentiate, partially losing their epithelial structure, to generate loose sclerotomal cells ventromedially. Sclerotomal cells migrate to surround the neural tube dorsally and notochord ventrally and undergo cartilaginous then bony differentiation, forming the vertebrae

spinal dysraphic conditions. However, it is not yet clear to what extent NC cells actually arise from the secondary neural tube in the low spinal region. Sensory ganglia are not formed at this level, suggesting a reduced differentiation repertoire of 'secondary' NC. The chick has a similar lack of sensory ganglia adjacent to the caudal-most levels of the secondary neural tube; NC cells arise, but their developmental potential is restricted to melanocytes and glia [17]. There is no information on NC origins and differentiation potential in the secondary neural tube region of mammalian embryos.

Vertebral Development Formation of the vertebral column proceeds in parallel with neural tube formation in the spinal region. Vertebrae arise from the paraxial mesoderm which is formed in the low spine by differentiation of NMPs in the tail bud region (see above). Paraxial mesoderm becomes segmented to form the epithelial somites, which are specified by a molecular oscillator that involves cyclical expression of a series of 'clock' genes in the paraxial mesoderm. Each cycle specifies a single somite on each side of the body and ensures the somites are regularly spaced [18]. During subsequent development, the somites partly lose their epithelial structure, forming loose sclerotomal cells ventrally that migrate around the notochord and neural tube, later undergoing cartilaginous and then bony differentiation (Fig. 21.2). Cells from the medial part of the sclerotome give rise to vertebral bodies and intervertebral discs, while the lateral regions of the sclerotome form the vertebral arches and ribs [19]. The caudal half of one sclerotome and the rostral half of the next together form a vertebral segment. Failure of the molecular oscillator to properly specify somites produces segmentation defects that alter number or size of vertebrae, whereas faulty sclerotomal migration around the neural tube and notochord is responsible for various malformations of the vertebrae.

Notochord During gastrulation, the rostral end of the primitive streak (the 'node') migrates caudally, leaving in its wake a midline population of cells called the 'head process', which intercalates into the hypoblast (primitive endoderm) layer, forming the definitive gut endoderm [20]. Cells in the midline of the head process 'pinch off' dorsally to form the notochord, a narrow rod-like structure situated between the neural tube and the gut. In humans, the notochord is considered to comprise rostral and caudal parts, separated by the 'primitive pit' that forms the 'neurenteric canal' through which the amniotic cavity communicates with the yolk sac cavity [21]. A neurenteric canal is not generally recognised in mouse development, where the notochord is a continuous, solid structure throughout its length, even though it has several distinct developmental origins [22]. Whether this is a human-mouse species difference is yet to be established. The notochord fulfills important roles, both as a signalling centre through its secretion of Shh, which induces and patterns the surrounding neural and mesodermal tissues, and as a 'nucleation' centre for sclerotomal cells to form the vertebral bodies. Ultimately the notochord forms the nucleus pulposus of the intervertebral discs [23].

Development of Closed Spinal Dysraphism: Clues from Animal Models and Human Genetics

The causes and pathogenesis of skin-covered spinal anomalies are poorly understood and in need of a concerted research effort. A prenatal origin is suggested by the frequent occurrence of these conditions in foetuses and young children, and most authorities consider the defects to be 'malformations', resulting from disturbed low spinal and vertebral development. However, an acquired pathogenesis, for example, involving vascular insults later in gestation, could apply in some cases

and should not be discounted as a possible mechanism. Here, we first review what is known about the developmental genetics of open NTDs, where there is a significant evidence base, and then consider our less complete knowledge of the embryonic development of closed spinal dysraphism.

Open NTDs and the Genetic Basis of Neural Tube Closure

The commonest types of human and mouse NTDs are anencephaly and myelomeningocele (open spina bifida) which arise from failure of primary neurulation in the cranial and spinal regions, respectively. Craniorachischisis, a rarer NTD variant in which most of the brain and the entire spine remains open, arises from failure of closure initiation (called Closure 1 in mice). The fact that the forebrain is often closed in foetuses with craniorachischisis points to an independent closure initiation site at the extreme rostral end of the neural plate, and this has been confirmed in both human [24] and mouse [25, 26] embryos. However, some other neural tube closure sites that were predicted for human embryos, based on examination of NTD patterns in late-stage foetuses [27], have not been confirmed in neurulation-stage embryos [24]. This reinforces the hazardous nature of 'backward extrapolation' to determine embryonic mechanisms.

Owing to the >200 genetic models of open NTDs in mice, we have a good understanding of the link between faulty neural tube closure and NTD development. Moreover, this genetic mouse resource has provided clues to the genes and pathways that may be critical for open NTD development in humans. For example, the close association of craniorachischisis with PCP gene mutations in mice has demonstrated the vital role of convergent extension in establishing a narrow, elongated neural plate to allow closure initiation. Genomic studies of PCP genes in humans with NTDs have also yielded positive findings: human foetuses with craniorachischisis were found to harbour mutations in the *CELSR1* and *SCRIB* genes of the PCP pathway [2].

Interestingly, individuals with later-arising NTDs have also been found to carry putative mutations in core PCP genes including *CELSR1*, *DVL1*, *DVL2*, *FZD6*, *PTK7*, *PRICKLE1*, *VANGL1* and *VANGL2* and in PCP-related genes including *DACT1*, *FUZZY*, *LRP6*, *SEC24* and *SCRIB* [28]. This suggests that PCP-dependent convergent extension plays a critical role throughout neural tube closure, not just at the start. Importantly, the patients are almost invariably heterozygous for a PCP gene variant, which is often transmitted from an unaffected parent. Mice heterozygous for PCP mutations are mostly unaffected (only homozygotes develop open NTDs), so it seems unlikely that a heterozygous PCP 'mutation' in humans can be solely responsible for an open NTD. This suggests that the PCP variants may interact with other, as yet unidentified, gene mutations to cause defects.

Other genes that are implicated in the causation of open NTDs in both mice and humans include those encoding enzymes of folate one-carbon metabolism which function in mitochondria. Around 70% of the cell's one-carbon units are generated in the mitochondria and then exported as formate to the cytoplasm, entering the

folate cycle to produce pyrimidines and purines for DNA synthesis. One-carbon units also enter the methylation cycle which transfers methyl groups to nucleic acids, proteins and lipids, for example, in the regulation of gene expression. Genes encoding enzymes of the glycine cleavage system, aminomethyltransferase (AMT) and glycine decarboxylase (GLDC), harbour a number of missense (i.e. amino acid-changing) genomic alterations in patients with open NTDs, but not in unaffected controls [3, 29]. In the case of *GLDC*, these variants diminish enzyme activity indicating a functional effect on folate metabolism. Both *Amt* and *Gldc* mouse mutants display NTDs and, strikingly, supply of exogenous formate to pregnant females prevents NTDs in *Gldc* mutant embryos [30]. Hence, disturbed mitochondrial folate metabolism is implicated in causation of open NTDs in mammals.

Spinal Cord Tethering: Incomplete Separation of the Secondary Neural Tube

As reviewed above, most of the spinal region (all post-cervical levels) develop by differentiation of neural and mesodermal lineages (and perhaps also endodermal) from a self-renewing population of neuro-mesodermal progenitors (NMPs) in the remnant of the primitive streak, called the 'tail bud' [31]. Spinal neural derivatives of the NMPs sequentially form the primary and then secondary neural tube. Hence, the very different morphology of open NTDs and closed dysraphic conditions must reflect the differing modes of neural tube morphogenesis, not the origin of the neuroepithelial cells which is closely similar in both.

'Tethering' of the spinal cord refers to the failure of the cord to 'ascend' normally during foetal and infant development [32]. Differential growth between spinal cord and vertebral column causes the conus to ascend from its original sacral level to the L2 vertebral level by adulthood. Moreover, the normal cord shows mobility with respiration, whereas this is lost in tethering; the result is that the terminal spinal cord and nerve roots become stretched, and neurophysiology is abnormal. In open spina bifida, failure of the primary neural tube to separate ('disjoin') from non-neural ectoderm (i.e. the future epidermis) results in tethering at the neural placode. This has been found to cause attenuation of spinal cord diameter immediately above the open lesion in mouse foetuses [33]. However, tethering is also frequently observed in closed dysraphism, where it seems likely that incomplete separation of the secondary neural tube from the surrounding tail bud tissue is responsible. A mesenchyme-to-epithelium transition (MET) occurs as the secondary neural tube forms [34], with genes becoming expressed that characterise the epithelial state, e.g. E-cadherin, while genes that typify mesenchyme are downregulated, e.g. fibronectin. It seems likely that failure to complete MET may underlie some cases of cord tethering in closed lesions. Additionally, other factors are known to contributing to cord tethering including the presence of abnormal lipoma tissue (see below), which can anchor the spinal cord to subcutaneous fat, and prevent spinal cord ascent.

Junctional Neurulation Disorders: Transition from Primary to Secondary Neurulation

In recent years, 'junctional neurulation defects' have been described in several unrelated patients where structurally and functionally normal primary and secondary neural tube derivatives are separated by a non-neural inert band [35, 36]. This striking phenotype has been related to the previous finding of a 'junctional neurulation zone' in the chick embryonic neural tube. Here, dorsal cells which express the neural marker Sox2 contribute to the caudal end of the primary neural tube while, at the same axial level, ventral Sox2-negative cells undergo epithelial-mesenchymal transition, migrate caudally and contribute to the secondary neural tube [37]. This finding corresponds to the dorsoventral demarcation at the primary-to-secondary 'transition zone' which was previously described for chick embryos, where the caudal end of the primary neural tube overlaps dorsally with the rostral end of the secondary neural tube ventrally [38]. However, no such transition zone occurs in the mouse embryo [15], raising a question about the relevance of this chick neurulation feature to humans. The gene *Prickle1* has been suggested to be essential for this junctional neurulation process, in view of its expression at this axial level and the neural tube defects that result from inhibition of *Prickle1* expression in the caudal region of chick embryos [37]. In mice, there are four *Prickle* genes, providing scope for functional redundancy. *Prickle1* has been shown to regulate body growth generally, with a partial loss-of-function phenotype resembling human Robinow syndrome [39], but with no low spinal dysraphic findings. To date, therefore, the mechanisms underlying these rare junctional neurulation defects in humans remain unexplained developmentally.

Spinal Lipoma: Possible Aberrant Differentiation of Neuromesodermal Progenitors

The ability of the self-renewing NMP cell population in the embryonic tail bud to differentiate into a variety of neural and mesodermal derivatives makes it a prime candidate for the origin of lumbosacral lipomas. Moreover, the recent development of methods to study NMP differentiation in culture offers an opportunity to define the differentiation signals that might divert such cells towards adipose development. An understanding of the in vivo origins of spinal lipoma, however, requires the development of an animal model, and only one has so far been described, as follows.

Ectopic expression of the gene *Gcm1* was achieved in the mouse tail bud by linking the *Gcm1* coding sequence to a *Hoxa7* enhancer and creating transgenic lines [40]. Expression of beta-galactosidase (encoded by the *LacZ* gene) confirmed that only low spinal expression of *Gcm1* occurred in the transgenic embryos (Fig. 21.3a–c). At late embryonic and foetal stages, several of the transgenic lines exhibited different dysraphic conditions including longitudinally duplicated spinal cord, resembling a split cord malformation, and caudally located open spina bifida.

Importantly, formation of a lipoma was described at the tip of the spinal cord (Fig. 21.3d–h), therefore providing a striking parallel to the situation in human closed spinal dysraphism.

The mammalian *Gcm1* gene is orthologous to the *glial cells missing* (*gcm*) gene of *Drosophila*, which functions as a master regulator of glial cell fate specification. Loss of *gcm* function in flies leads to a paucity of glia whereas increased *gcm* expression induces ectopic glia. Strikingly, the mammalian *Gcm1* gene can substitute for the *Drosophila* version in fly development, arguing for a high level of conservation of function. *Gcm1* is a transcription factor that activates *Hes* genes [41] which mediate the downstream effects of Notch signalling, in regulating neural stem cell fate. In the *Gcm1* transgenic mice, *Notch1* and *Tbx6* were downregulated, which was interpreted as allowing more cells than normal to assume a neuroepithelial fate. However, the observation of ectopic lipoma formation in this model, in conjunction with structural defects of the low spinal neural tube (both primary and secondary), argues strongly for a more extensive maldifferentiation of NMPs and is consistent with a fundamental defect of progenitor cell differentiation leading to spinal lipoma in humans.

Other explanations have been suggested for the origin of lumbosacral lipomas. For example, the theory of 'premature dysjunction' suggests that neural and non-neural ectoderm separate before closure of the neural tube, thus allowing paraxial mesoderm to migrate into the open neural tube preventing closure and differentiating into fat cells [42]. However, an experimental test of this idea in the chick embryo, involving surgical incision of a unilateral neural fold, gave variable developmental anomalies but no histologically identified lipoma formation [43].

Sacrococcygeal Teratoma: Multi-Lineage Differentiation from a Caudal Progenitor Cell

As the most frequent congenital teratoma, and with a caudal location, sacrococcygeal teratomas have long been suggested to arise from the embryonic tail bud. Even before the demonstration of a caudally located NMP progenitor cell population, experiments both in vivo and in vitro demonstrated that the chick and mouse tail buds are capable of differentiating into tissues characteristic of all three germ layers [34, 44]. Moreover, there is a clinical association between sacrococcygeal teratomas and lumbosacral lipomas [45], consistent with a developmentally linked origin. It remains to be determined, however, under what developmental circumstances a multi-germ layer, teratomatous differentiation pattern would occur, as opposed to a highly specific maldifferentiation in which adipocyte formation is the primary pathogenic outcome.

A parallel to sacrococcygeal teratoma comes from recent studies of chordoma, a low-grade but highly recurrent tumour that typically occurs around 50–60 years of age. Chordoma originates in cells remaining from the embryonic notochord, and cell-fate-tracking experiments in mice have identified notochordal cell remnants

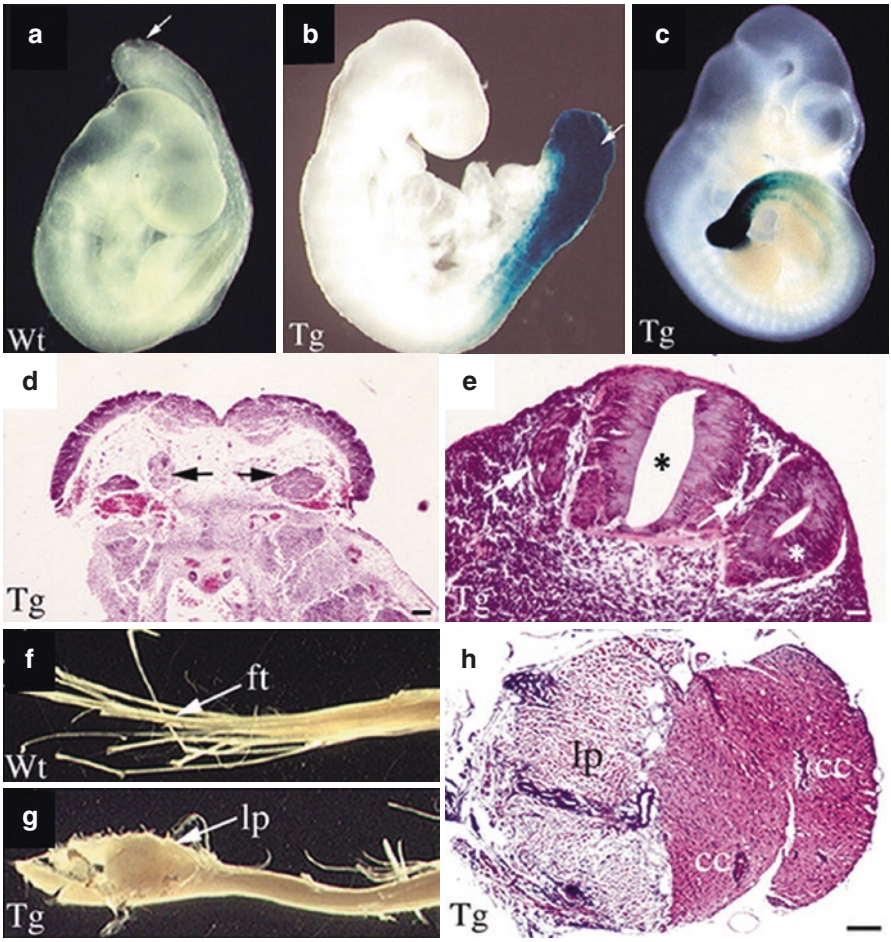

Fig. 21.3 Ectopic expression of the *Gcm1* gene, under control of a *Hoxa7* enhancer sequence, causes mice to develop open and closed neural tube defects, with caudal lipoma. (**a**–**c**) Expression of β-galactosidase, encoded by the transgene, at embryonic days (E) 9.5 (**a**, **b**) and 10.5 (**c**). Staining is observed in the caudal region with an anterior boundary at the level of somites 18–20, in transgenic (Tg) embryos (**b**, **c**) but not in a non-transgenic control (Wt). Arrows indicate the closing region of spinal neural tube (the posterior neuropore) at E9.5 (**a**, **b**), whereas the spinal neural tube is closed at E10.5 (**c**). (**d**–**h**) Developmental anomalies in mice ectopically expressing the *Gcm1* transgene. Transverse sections through the lumbosacral level at E12.5 show open spina bifida (**d**) and split cord (**e**; asterisks). Dorsal root ganglia are indicated by the arrows. Views of the filum terminale (ft) in 1-month-old wild-type (**f**) and transgenic (**g**) spinal cords show the presence of a lipoma (lp) in the transgenic spinal cord (**g**). Transverse section of the adult transgenic spinal cord (**h**) shows the attached lipoma and the split cord, with central canals (cc) marked. (**d**, **e**, **h**) Haematoxylin and eosin staining. Bars: 0.1 mm. (Modified from Nait-Oumesmar et al. [40]; with permission)

[46] whose distribution matches the sites where chordomas typically arise (skull, mobile spine and sacrum). Genetic studies show that the gene *Brachyury*, which is essential for mesoderm formation generally and for notochord development specifically, is duplicated in familial chordoma [47], consistent with the finding that sporadic chordomas typically overexpress *Brachyury* [48]. Hence, the origin in adulthood of a tumour arising from embryonic cell remnants is the result of overexpression of a gene necessary for formation and maintenance of the same tissue in embryogenesis. Analogous over-activation of one or more embryonic pathways might prove to be implicated in spinal dysraphic conditions, and sacrococcygeal teratoma is perhaps a prime candidate.

Sacro-caudal Agenesis: Premature Arrest of Axial Elongation

The spinal axis grows caudally throughout the time that the primary and then secondary neural tube are forming. However, this caudally directed growth can become arrested at almost any stage, generating body axial truncation. In humans, this is most often encountered as sacral agenesis (also called 'caudal regression syndrome'), which can be isolated, associated with maternal diabetes mellitus or as part of a recognised syndrome including OEIS complex, VACTERL association and Currarino triad. In each case, it seems likely that the axial arrest has its origin in a defect of the developing tail bud. This contrasts with the origin of another caudal malformation, sirenomelia, in which the caudal axis is grossly abnormal with failure of lower limb separation. This can be strongly associated with an aberrant abdominal umbilical artery that arises from the aorta, suggesting a 'vascular steal' condition, involving redirection of blood flow from the lower extremities during development [49].

The genetic and cellular requirements for axis elongation during spinal development have been well established through analysis of mouse, chick, amphibian and fish models. In mice, continued proliferation of the NMP cell population is vital, as this is the source of cells for newly formed axial levels. NMP proliferation and multipotency depend on *Wnt3a* and *Fgf8* gene function. Wnt3a is a ligand for canonical Wnt signalling, necessary for cell proliferation and mesodermal differentiation, in part by regulation of Fgf8-mediated signalling via its receptor Fgfr1. Null mutations in either *Wnt3a* or *Fgf8* result in body axis truncation, as does excessive retinoid (vitamin A derivative) exposure, which inhibits Wnt3a expression and leads to precocious cell differentiation within the tail bud. A similar outcome is seen when the retinoid-metabolising enzyme Cyp26a1 is mutated [50], reflecting the need for the tail bud to maintain low endogenous retinoid levels for continued NMP 'stem cell' behaviour. Embryos developing in a diabetic maternal environment are predisposed to this retinoid-mediated axial truncation [51].

It remains to be determined whether axial truncation phenotypes in humans similarly reflect defects in WNT/FGF/retinoid pathways as in mice. One issue to be borne in mind is that the mouse is a tailed mammal, so that axial truncation with absent tail is extremely obvious. In humans, while a caudal appendage is formed in

the embryo, this is entirely reabsorbed into the body during subsequent development. Hence, some caudal defects of axial elongation may be less obvious in humans than in mice.

Split Cord Malformations

Split cord anomalies are regularly observed in humans and occur in a number of mouse genetic mutants [52]. Strikingly, when mouse tail bud development is arrested, the default pathway of NMP differentiation is neural, with formation of multiple neural tubes. These can exist in a chaotic arrangement, for example, after retinoid-induced arrest of axial elongation [53], or as a precisely organised structure, as in mice lacking the *Tbx6* gene where bilateral ectopic neural tubes form instead of somites either side of the midline neural tube [54]. Other genes whose mutants exhibit duplicated neural tube [52] include *Wnt3a* (the vestigial tail mutant), *Axin1* (the Fused and Kinky mutants) and *Brachyury* (the T mutant). All of these genes are required for mesodermal differentiation of NMPs, providing strong evidence to implicate faulty NMP development in the origin of split cord. Additionally, convergent extension may also play a role, as when faulty this can produce a broad, sometimes bifurcated notochord in mice with PCP gene mutations [55]. In humans, it has been suggested that split cord malformations result from adhesions between ectoderm and endoderm that lead to an accessory neurenteric canal around which an endomesenchymal tract condenses, bisecting the developing notochord. This is seen as causing formation of two hemineural plates [56] sometimes with pre- and post-vertebral enteric cysts, posterior enteric sinus and posterior enteric remnants [57]. These hypotheses remain to be tested experimentally.

Currarino Syndrome: An Emerging Gene Regulatory Network

A phenotype related to caudal regression syndrome occurs in the Currarino triad which comprises a sickle-shaped sacrum, presacral mass (either teratoma or anterior meningocele) and anorectal anomaly [55]. In practice, only one in five cases exhibits all three of these features, while associated malformations include Hirschsprung's disease and renal and gynaecological anomalies [58]. The occurrence of familial cases exhibiting autosomal dominant inheritance has led to the identification of mutations in the *MNX1* gene (also called *HLBX9*) which encodes a homeodomain-containing transcription factor [59]. As regards animal models, a knockout mouse lacking *Mnx1* was developed, and while this exhibited pancreatic defects, revealing a role for the gene in foregut development [60], no caudal developmental disorders were observed. Other genes of interest are *Pcsk5* and *Gdf11*, whose loss-of-function phenotypes include VACTERL/caudal regression/Currarino-like malformations [61]. Pcsk5 is a proprotein convertase that cleaves and activates Gdf11 protein, regulating downstream genes including *Mnx1* and caudally expressed *Hoxa*, *Hoxc* and *Hoxd* genes; these members of the *Hox* gene family specify levels

along the body axis [62]. *Pcsk5* and *Gdf11* expression was inhibited in the hindgut region of mouse embryos after retinoid treatment that induced a caudal regression phenotype [63]. Non-synonymous mutations in *PCSK5* were found in patients with VACTERL syndrome [62]. Hence, a gene regulatory network is emerging that is necessary for normal caudal development, although the precise developmental events that these genes regulate remain unclear.

Vertebral Defects: Faulty Specification and Migration of Sclerotomal Cells

Incomplete neural arches of one to two successive vertebrae (most commonly L5 and S1), called spina bifida occulta, affects 10–15% of the population and is generally asymptomatic. However, of greater severity is a range of variable vertebral disorders that are often detected in patients with closed dysraphism, including more extensive dorsal spina bifida, butterfly vertebrae, hemivertebrae and vertebral fusions. These are often found as part of multisystem malformation syndromes, for example, with butterfly vertebrae in Alagille syndrome, caused by mutations in JAG1 or NOTCH2 genes, and hemivertebrae with vertebral fusions in spondylocostal dysostosis (also called Jarcho-Levin syndrome).

While anomalies of neural tube formation typically have secondary effects on subsequent vertebral development, a number of genes have roles specifically in vertebral development, independently of the neural tube. For example, isolated dorsal spina bifida of the entire spinal column occurs in the presence of normal spinal neural tube formation in the *Patch* mutant mouse [64] that lacks platelet-derived growth factor receptor alpha (*Pdgfra*). The posterior neural arch elements develop initially, but fail to undergo appropriate condensation. Similarly, the transcription factor gene *Zic1* is required for formation of the posterior vertebral elements, with a particularly strong dorsal spina bifida phenotype (with no neural tube involvement) in double mutants with *Gli3*, a downstream gene in the *Shh* pathway [65].

A second group of genes is required for ventral vertebral development and pedicle formation. ‘Anterior’ (i.e. ventral) vertebral spina bifida occurs in cases where the vertebral bodies are malformed or absent (butterfly vertebrae) and several genes produce this phenotype in mice. Loss of function of *Pax1*, a member of the Pax (Paired box) transcription factor family, causes abnormal or absent vertebral bodies and intervertebral discs. The proximal parts of ribs are also defective, whereas the neural arches are essentially normal [66]. A second mouse model is provided by the *Bapx (Nkx3.2)* mouse mutant which also lacks vertebral bodies [67]. Regulation of *Bapx* is under control of both *Pax1* and *Shh* [68], providing evidence for key regulatory pathways in vertebral body and intervertebral disc development. A third genetic function is required for development of the pedicles and transverse processes. *Uncx4.1* gene mutants die perinatally and exhibit severe malformations of the axial skeleton in which the pedicles, transverse processes and proximal ribs are lacking along the entire length of the vertebral column [69].

Hence, development of each part of the sclerotome that gives rise to the different parts of the vertebrae is under distinct genetic control, and mutations in these key signalling pathways are strong candidates for vertebral malformations in humans.

Conclusions

This review has attempted to apply the principles that are emerging in vertebrate developmental biology and genetics to the diverse anomalies that comprise human closed spinal dysraphism. Our understanding is currently fragmentary, with a few areas having a strong experimental evidence base, and many others remaining hypothetical. A future concerted research effort is needed to bring together clinical observations with research in developmental biology. This should significantly advance knowledge in this important area in the coming years.

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