

Review Article

Embryology of the spine and associated congenital abnormalities

Kevin M. Kaplan, MD^{a,*}, Jeffrey M. Spivak, MD^{a,b}, John A. Bendo, MD^{a,b}

^aNew York University-Hospital for Joint Diseases, Department of Orthopaedic Surgery, 14th Floor, 301 East 17th Street, New York, NY 10003, USA

^bHospital for Joint Diseases Spine Center, Department of Orthopaedic Surgery, 14th Floor, 301 East 17th Street, New York, NY 10003, USA

Received 11 June 2004; accepted 18 October 2004

Abstract

BACKGROUND CONTEXT: The spine is a complex and vital structure. Its function includes not only structural support of the body as a whole, but it also serves as a conduit for safe passage of the neural elements while allowing proper interaction with the brain. Anatomically, a variety of tissue types are represented in the spine. Embryologically, a detailed cascade of events must occur to result in the proper formation of both the musculoskeletal and neural elements of the spine. Alterations in these embryologic steps can result in one or more congenital abnormalities of the spine. Other body systems forming at the same time embryologically can be affected as well, resulting in associated defects in the cardiopulmonary system and the gastrointestinal and genitourinary tracts.

PURPOSE: This article is to serve as a review of the basic embryonic development of the spine. We will discuss the common congenital anomalies of the spine, including their clinical presentation, as examples of errors of this basic embryologic process.

STUDY DESIGN/SETTING: Review of the current literature on the embryology of the spine and associated congenital abnormalities.

METHODS: A literature search was performed on the embryology of the spine and associated congenital abnormalities.

RESULTS: Development of the spine is a complex event involving genes, signaling pathways and numerous metabolic processes. Various abnormalities are associated with errors in this process.

CONCLUSION: Physicians treating patients with congenital spinal deformities should have an understanding of normal embryologic development as well as common associated abnormalities.

© 2005 Elsevier Inc. All rights reserved.

Keywords: Embryology; Spine; Congenital; Abnormalities

Embryology of the spine

Development of the body's form begins during gastrulation, a process in which a trilaminar embryonic disc is created from a bilaminar disc (Fig. 1). The primitive streak, well-defined germ layers and the notochord develop during gastrulation, which usually occurs during the third week of gestation. It is well known that the notochord and somites are the most significant structures responsible for the development of the future vertebral column [1].

Epiblastic cells migrate from the deep surface of the primitive streak and form the embryonic endoderm (Fig. 2). Subsequently, cells continue to migrate from the primitive streak, creating the embryonic mesoderm. The cells that remain on the epiblastic side of the embryonic disc form the embryonic ectoderm. Several embryonic growth factors are thought to induce the migration of these cells from the primitive streak [2,3]. Cell migration continues into the fourth week of development after which the primitive streak regresses and disappears in the sacrococcygeal region [4].

A group of specialized cells that migrate through the primitive node, which is located at the cranial end of the primitive streak, gives rise to the prechordal plate and notochordal process (Fig. 3). Cells migrate in from all areas of the primitive node. However, the cells migrating most anteriorly form the prechordal plate, whereas the ones migrating most posteriorly form the notochordal process [4].

FDA device/drug status: not applicable.

Nothing of value received from a commercial entity related to this manuscript.

* Corresponding author. 245 East 24th Street, Apt. 10A, New York, NY 10010, USA. Tel.: (917) 880-1882; fax: (212) 598-6793.

E-mail address: kaplak02@med.nyu.edu (K.M. Kaplan)

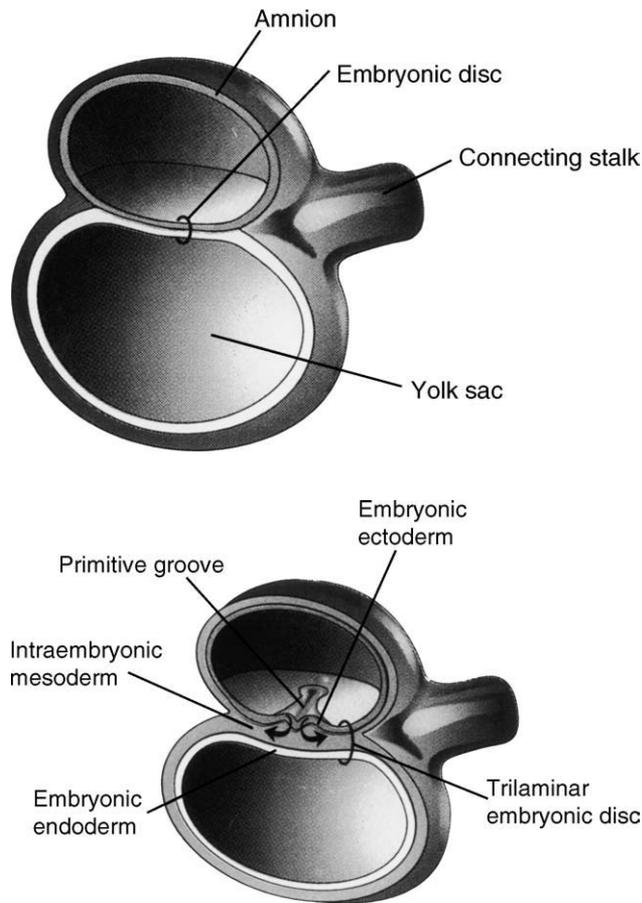


Fig. 1. (Top) The bilaminar embryonic disc surrounded by the amnion and yolk sac. (Bottom) During gastrulation, a trilaminar disc forms from the bilaminar disc creating the model for the future ectoderm, mesoderm and endoderm. (Reprinted from Moore K, Persaud TVN, *The developing human: clinically oriented embryology*, 6th ed., 1998, with permission from Lippincott Williams & Wilkins.)

The prechordal plate has several functions, including prevention of anterior migration of the notochordal process by remaining adherent to the surface ectoderm [1]. The notochordal process develops into the notochord and will be an early representation of the future vertebrae and bony skeleton. In addition, Nolting et al. [5] has described the importance of the notochord in various signaling pathways during embryonic development. Although beyond the scope of this review, there has been a tremendous amount of research in the last decade in order to further define the molecular cascade involved in spinal development [6]. Alterations in this cascade may have an impact on the normal embryologic development of the spine.

Formation of the notochord occurs through a complex series of events. As previously stated, cells migrating through the primitive node form the notochordal process. These cells eventually fuse with the endodermal cells of the yolk sac, creating an opening between the yolk sac and amnion. However, the remaining cells of the notochordal process align themselves to create a notochordal plate, which

will subsequently fold to form the notochord containing a central canal [4] (Fig. 4).

On both sides of the notochord, the mesoderm differentiates into three main areas: paraxial, intermediate and lateral mesoderm [4] (Fig. 4). Forty-two to 44 pairs of somites will form from the paraxial mesoderm by the end of the fifth week. Development of the somites occurs in a craniocaudal fashion and will eventually help in forming the bones of the head, vertebrae, other bony structures of the thorax and associated musculature. The number of somites can be used to estimate embryonic age.

Each somite develops into two parts: a sclerotome and a dermomyotome. The cells of the sclerotome are responsible for the formation of the spine, and the dermomyotomes form muscle cells and the overlying dermis of the skin [4].

During the fourth week, cells of the sclerotome begin to migrate toward and around the notochord and neural tube. Migration of these types of cells not only depends on specific molecular processes but also on the normal growth of surrounding structures [7–9]. Once the sclerotomes have surrounded the notochord and neural tube, each level will separate into a cranial area of loosely packed cells and a caudal area of densely packed cells. The intervertebral disc will form between these two layers of cells (Fig. 5). However, at this point in development, O’Rahilly [1] describes the area between the two halves in one level of the sclerotome as a “cell-free space.”

Neural development will be discussed later in this review, but it is important to note that at this stage the spinal nerve is associated with the caudal area of the sclerotome, and the intersegmental artery is located either between the somites or directly apposing the caudal area [1]. As development continues, this pattern will serve as a model for future segmentation and differentiation of the nervous system and blood supply for the body. The “cell-free space” will fill with cells migrating cranially from the caudal densely packed sclerotome layer to form the annulus fibrosus [10]. The nucleus pulposus will develop inside the annulus from notochord that does not deteriorate. The developing intervertebral disc divides each sclerotome level and forces the remaining cells from a given densely packed layer to fuse with the loosely packed cells of the adjacent caudal level. Thus, as O’Rahilly describes, one complete vertebra requires two somites to interact properly with each other in order to develop normally [1]. After fusion, arteries cross vertebral bodies while the spinal nerves remain between them [4]. Failure of this proper segmentation may result in a congenital abnormality.

Fusion of parts of the adjacent sclerotomes creates the centrum, which further develops into the vertebral body. The centrum allows bone to continually develop around it. The cells that initially migrated adjacent to the neural tube, rather than the notochord, develop into the neural arches, which serve to protect the spinal cord, vessels and nerve roots, before leaving through the intervertebral foramina [4] (Fig. 6). Vertebral arches consist of two pedicles and left

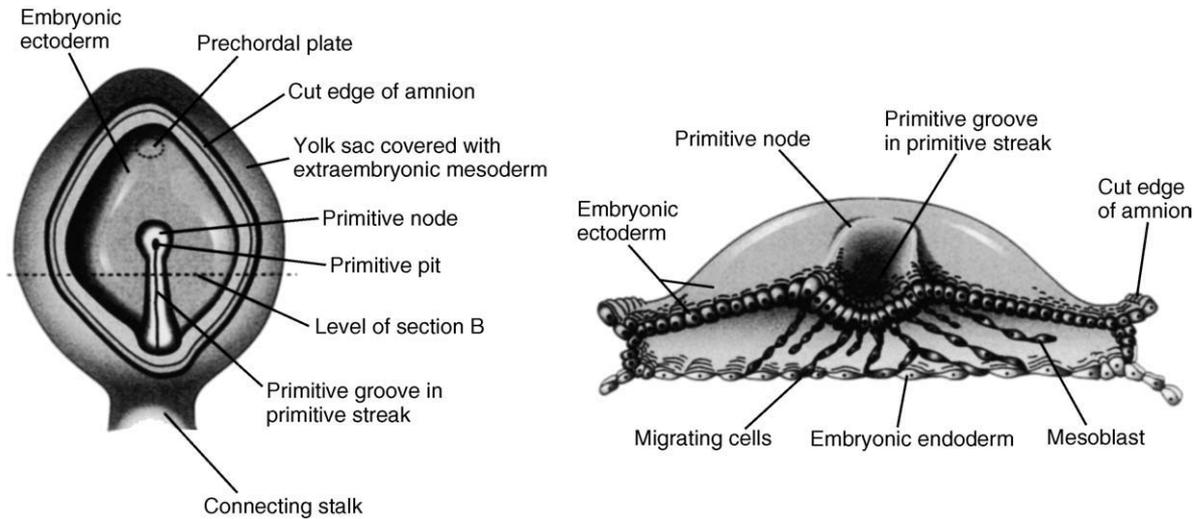


Fig. 2. Cells migrate in from the primitive streak. The deepest cells form the endoderm, followed by the mesoderm, while the remaining cells form the ectoderm. (Reprinted from Moore K, Persaud TVN, *The developing human clinically oriented embryology*, 6th ed., 1998, with permission from Lippincott Williams & Wilkins.)

and right halves of the laminae. The other processes associated with the posterior vertebral arch include the spinous process, transverse processes and articular processes. Anatomical differences exist between the vertebrae found at different levels [11]. The centrum and the two halves of the vertebral arches develop separately and must fuse to one another. The spinal column is made of seven cervical vertebrae, twelve thoracic vertebrae, five lumbar vertebrae, the sacrum and the coccyx. The spinal nerves exit between the vertebrae through intervertebral foramina to provide innervation throughout the body.

During the sixth week, after cells have migrated and vertebral structures begin to fuse, signals from the notochord and neural tube induce the chondrification of the relevant structures [1]. After chondrification, ossification will begin after which the notochord will disintegrate.

Ossification centers can be found in three main areas in the vertebrae: one in the centrum and one on each side of the vertebral arch (Fig. 7) [4]. The centrum or vertebral body will articulate with the vertebral arch at the neurocentral joints at birth, with fusion occurring between the ages of 5 and 8 years. The two pieces of the arch begin to fuse during the first year of life with complete fusion occurring by age six years [4]. Moore describes the five secondary ossification centers that form after birth; one for the tip of each transverse process, one for the extremity of the spinous process, one for the upper and one for the lower surface of the body [4]. It is important to mention that bone ossified from the secondary centers will contribute to the formation of growth plates. It is the absence and asymmetry of growth plates that may contribute to a congenital defect. In addition, defects in both chondrification and ossification cause several of the most common congenital abnormalities.

Molecular signals from the notochord are responsible for differentiation and, eventually, chondrification and ossification of the vertebrae [5]. The notochord along with several genes and the signaling pathways with which they are involved enable the proper development of the vertebrae and the nervous system.

The nervous system of the embryo is derived from the surface ectoderm of the trilaminar disc and begins to develop during the third week. Several genes and specific molecular signals from the notochord and mesoderm are capable of inducing the formation of the neural groove. The neural groove will fold into a tube and represents the future

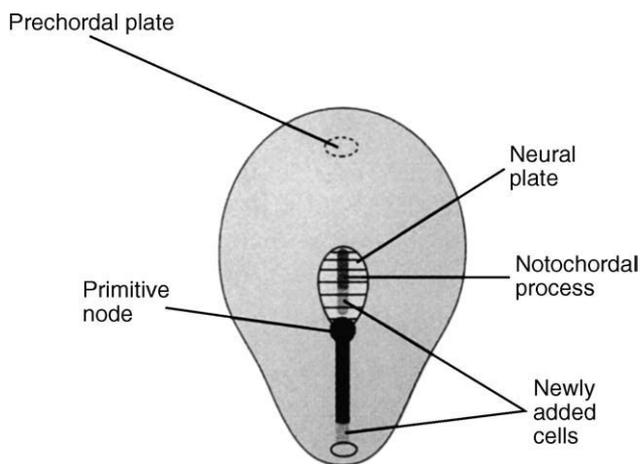


Fig. 3. Specialized cells migrate through the primitive node to help form the prechordal plate and notochordal process. The notochordal process serves as an early representation of the vertebrae and bony skeleton. (Reprinted from Moore K, Persaud TVN, *The developing human clinically oriented embryology*, 6th ed., 1998, with permission from Lippincott Williams & Wilkins.)

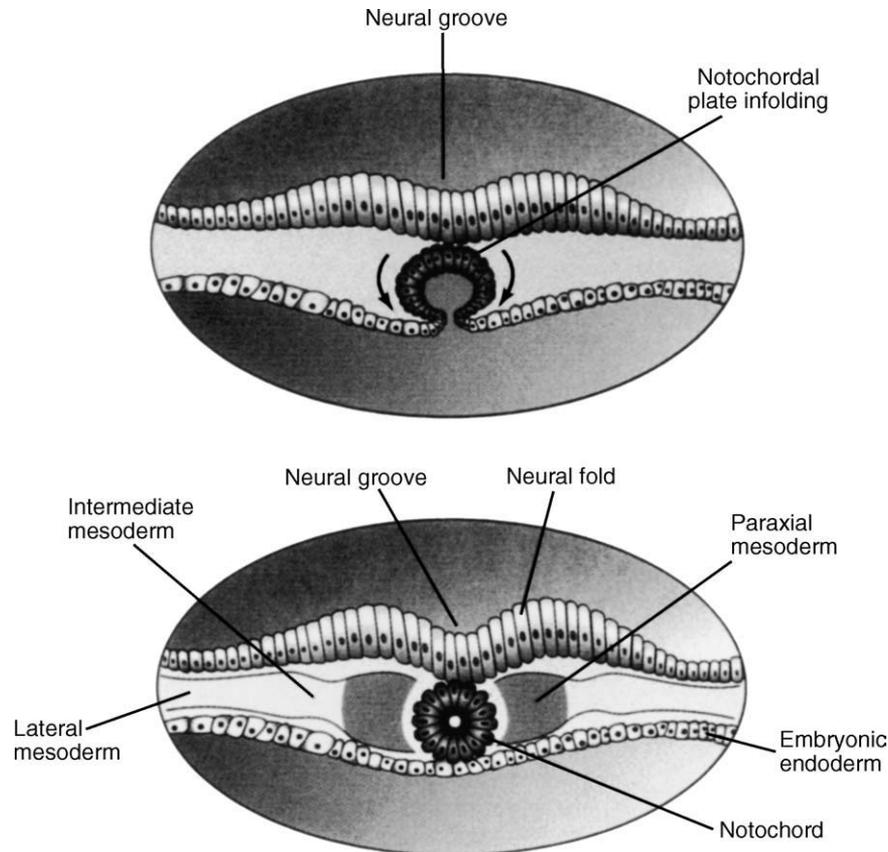


Fig. 4. The notochordal plate folds into the notochord after which the mesoderm surrounding this structure differentiates into the paraxial, intermediate and lateral mesoderms. Further differentiation creates 42 to 44 pairs of somites from the paraxial mesoderm. (Reprinted from Moore K, Persaud TVN, *The developing human clinically oriented embryology*, 6th ed., 1998, with permission from Lippincott Williams & Wilkins.)

central nervous system (Fig. 4). Weston [12] describes how the peripheral nervous system develops from neural crest cells that migrated during the folding process. The brain develops from the most cranial aspects of the neural tube, and the spinal cord develops from the remaining caudal areas. Pia mater, arachnoid mater and dura mater surround and protect the spinal cord. The pia and arachnoid mater are both neural crest in origin, whereas the dura mater is mesenchymal in origin. In an embryo, the spinal cord fills the canal, but as a result of normal growth and development, it will eventually change positions [12].

O'Rahilly states that development in the caudal areas of the nervous system promotes spinal cord ascension from the sacrum into the lumbar region, typically around level three [1]. After birth, as a child develops, the spinal cord will continue to ascend to the level of the first or second lumbar vertebra. The remaining caudal aspect of the spinal canal becomes a conduit for the lumbar and sacral nerve roots referred to as the cauda equina. Nerve roots leave the spinal cord at angles as a result of the normal spinal cord ascension [1].

During the fetal period, the normal curve of the vertebral column is kyphotic [12]. This primary curvature continues within the thoracic region throughout development to maturity. However, the cervical and lumbar lordotic curvatures

develop secondarily during infancy. O'Rahilly argues that the cervical curve begins during fetal life, but agrees that the majority of development occurs after birth [1]. Lordosis in the cervical vertebrae develops as a result of the infant holding its head upright. Lumbar lordosis similarly develops secondarily as a result of the infant achieving a sitting and then standing posture.

Concurrent development of additional organs and systems

Paraxial mesoderm is responsible for the formation of the vertebrae as well as the dermis of the skin, striated skeletal muscle, muscles of the head and connective tissue [4]. In addition, the other two areas of mesoderm, intermediate and lateral, are involved in the development of the urogenital, pulmonary and cardiac systems. Thus, a defect affecting the development of the mesenchyme responsible for bony formation of the spine may also be responsible for defects in alternative organ systems. As will be discussed, causes for congenital defects may involve a variety of factors, but numerous studies have led to the conclusion that specific systems are intimately related to the development of the spine.

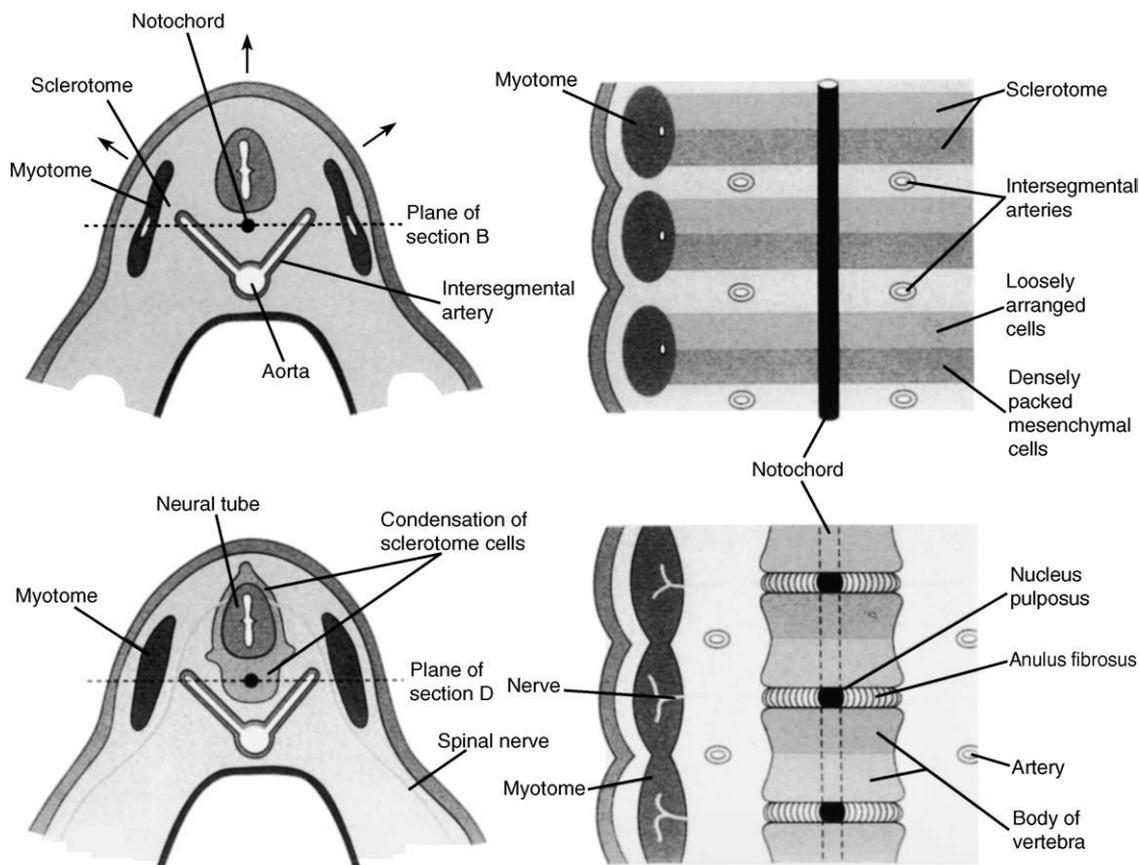


Fig. 5. Somites differentiate into sclerotome and dermomyotome. Cells of the sclerotome begin to migrate toward and around the notochord and neural tube. Once the sclerotomes have surrounded the notochord and neural tube, each level will separate into a cranial area of loosely packed cells and a caudal area of densely packed cells. The intervertebral disc will form between these two layers of cells. (Reprinted from Moore K, Persaud TVN, *The developing human clinically oriented embryology*, 6th ed., 1998, with permission from Lippincott Williams & Wilkins.)

Studies have estimated a 30% to 60% incidence of additional abnormalities in children with an existing congenital spinal deformity [13]. The main associated defects involve the VACTERL syndrome. VACTERL is an abbreviation with each letter representing an associated defect; vertebral anomalies, imperforate anus, cardiac abnormalities, tracheoesophageal fistula, renal dysplasias and limb malformations [14]. Another classic syndrome associated with congenital spinal defects is Klippel-Feil, which will be discussed in this review. Various intraspinal abnormalities may also be observed in these patients. In addition, several other structural abnormalities may be associated, including preauricular ear tags, mandibular hypoplasia, cleft lip, cleft palate and absent uterus or vagina.

The genitourinary system may be the most frequently involved system with congenital abnormalities of the spine. MacEwen et al. [15] reports a 20% incidence of urinary tract anomalies in studies on patients with congenital spinal abnormalities. Evidence supporting his findings stems from the fact that the mesoderm forming the vertebrae is also responsible for the formation of the mesonephros, the predecessor of the mature genitourinary system. The medial region of this mesoderm forms the vertebrae while the ventrolateral region forms the mesonephros. Many of the abnormalities

that arise in the genitourinary system do not need treatment. However, MacEwen et al. [15] reports that 6% of patients may have a clinically significant anomaly.

The cardiopulmonary system may be compromised by a congenital spinal abnormality. Several studies have indicated a higher incidence of congenital heart defects in patients with congenital spine anomalies, and many patients may have difficulty with respiration because of abnormal curvatures of the spine. These anomalies may also be fatal and should be diagnosed and treated before these problems progress.

Abnormalities of the spine have the potential to affect the spinal cord and associated nerve roots. Neurological symptoms can range from minor motor or sensory signs to paraplegia, depending on the type and severity of the abnormality [16].

Classification of congenital abnormalities

When discussing congenital abnormalities, it is important to identify the type of malformation, the resulting deformity and the specific region of the spine where the malformation occurs [17]. Malformations of the spine can be classified

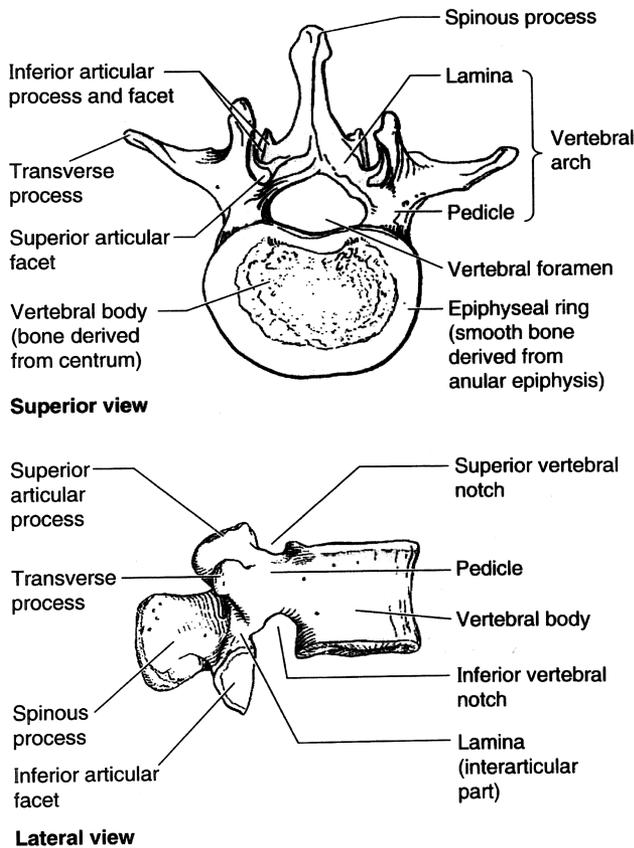


Fig. 6. A normal vertebra. (Reprinted from Moore K, Clinically oriented anatomy, 1999, with permission from Lippincott Williams & Wilkins.)

into three main groups: neural tube defects, defects of segmentation and defects of formation (Fig. 8). As discussed in previous sections, mesenchyme creates the model for the bony structures, while signals from the notochord induce

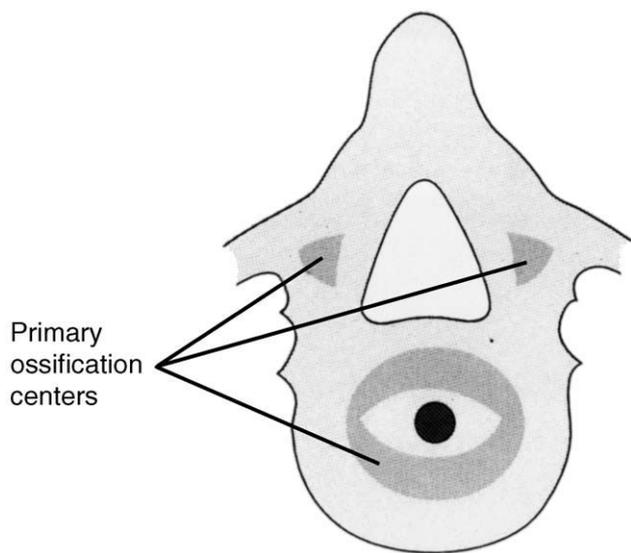


Fig. 7. Ossification centers found in each vertebra. (Reprinted from Moore K, Persaud TVN, The developing human clinically oriented embryology, 6th ed., 1998, with permission from Lippincott Williams & Wilkins.)

normal bony development. Abnormal mesenchyme, an abnormal notochord and genetic abnormalities affecting signaling can predispose a fetus to abnormal development of the bony skeleton. These developing congenital anomalies of the spine seen clinically can be a result of one or a mixture of the aforementioned defects.

Neural tube defects, failures of formation and failures of segmentation

A neural tube defect refers to a condition in which the neural tube fails to completely close during the fourth week of embryonic development [4]. As a result, structures overlying these midline abnormalities are severely affected and may be unable to form. Many theories have surfaced as to the causes of neural tube defects, and several studies suggest that nutritional and environmental factors may promote these defects. In addition, certain drugs, such as anticonvulsants, may increase the chance of a neural tube defect. These studies have also suggested that prophylaxis with vitamins and folic acid may reduce the chances for such defects [18]. Finally, other studies suggest that neural tube rupture may cause a neural tube defect as well as various other congenital abnormalities. In-utero diagnosis of a neural tube defect may be considered when there is an elevated level of alpha-fetoprotein [19].

Failures of formation arise as a result of an absence of a structural element of a vertebra. Any region of the vertebral ring may be affected: anterior, anterolateral, posterior, posterolateral and lateral. The type of deformity depends on the area of the vertebral ring affected, which will alter normal growth patterns. Typical observable defects are hemivertebrae or wedge vertebrae [13] (Fig. 8).

Hemivertebrae are bony remnants that did not complete normal development and can be fully segmented, semisegmented or nonsegmented. Segmented hemivertebrae still have growth plates both cranially and caudally. Fusion with a cranial or caudal vertebra creates the semisegmented hemivertebra. Thus, in a semisegmented vertebra, there is a functional disc on one side only. A nonsegmented vertebra has not separated from either the cranial or caudal vertebra. With lower growth potential, this situation usually has less overall effect on the contour of the spine and the scoliosis is less likely to progress during growth.

When both the cranial and caudal vertebrae conform in shape to make room for the hemivertebra, the anomalous vertebra is referred to as incarcerated. Incarcerated hemivertebrae may not affect the shape of the spine. The pedicles of an incarcerated hemivertebra are in line with the curve created by the pedicle cranial and caudal to it. A nonincarcerated hemivertebra is always fully segmented, and the potential wedge effect of these anomalies results in a higher likelihood of progression [20]. In this case, the pedicles are outside of the pedicle line of the adjacent vertebrae. Multiple hemivertebrae on the same side are considered

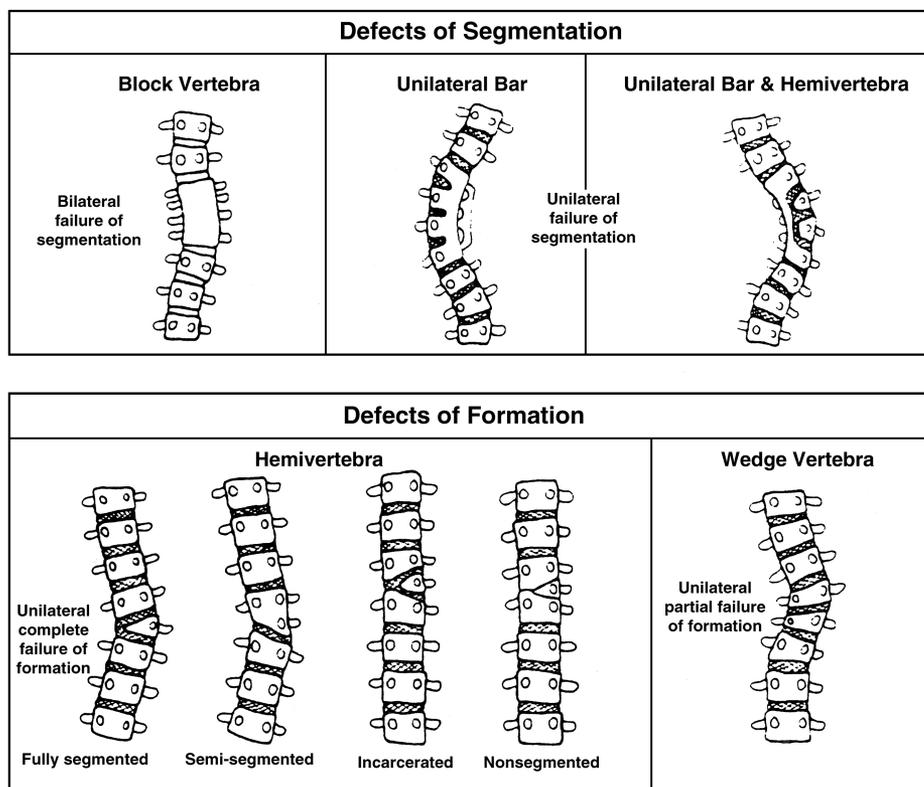


Fig. 8. Defects of segmentation and formation. (Reprinted from Weinstein SL, ed. *The pediatric spine*, 2nd ed., 2001, with permission from Lippincott Williams & Wilkins.)

severe defects, whereas those on opposite sides are less severe and may act as counterbalances. A wedge vertebra usually involves a unilateral partial failure of formation of one of the chondrification centers [13].

Failures of segmentation occur when two or more vertebrae fail to fully separate and divide with concomitant partial or complete loss of a growth plate (Fig. 8). Embryologically, if two adjacent somites or their associated mesenchyme do not separate properly, a segmentation defect will occur. These defects are classified depending on the region and quantity of vertebrae affected. Involvement of entire vertebrae creates block vertebrae, whereas defects of specific regions of the vertebral ring create unilateral bars that act as an asymmetric rigid tether to normal growth [17]. It is also possible to have a bilateral failure of segmentation and unilateral unsegmented bars with a contralateral hemivertebra [13].

Defects of formation and segmentation are not necessarily mutually exclusive. Often, an individual case is a mixture of a failure of formation and a failure of segmentation, creating complex structural abnormalities. Given the possibility and mechanism of embryological malformations, it is important to note that manifestations of these abnormalities are seen clinically as a result of normal growth of the surrounding structures.

Because of the fact that most of the common abnormalities have a multifactorial etiology, it is difficult to identify one factor that may be responsible. However, research has

confirmed various possible causes, which may help in the prevention of these anomalies.

Fetal exposure to thalidomide during critical stages of development is a well-known cause of severe congenital malformations. These abnormalities are indistinguishable from those associated with nonthalidomide cases. In addition, Ghidini et al. [21] published a case report suggesting that mothers taking lovastatin have shown increased risks for congenital abnormalities. Further studies by Nora et al. [22] have shown that certain progesterone/estrogen compounds may increase the incidence of these anomalies. In brief, a physician must recognize that the majority of these abnormalities have a multifactorial basis with current research implicating a variety of possible etiological agents.

Spina bifida

Spina bifida is the most common neural tube defect, resulting from the failure of the fusion of the embryonic vertebral arches. The type of spina bifida is determined by the pattern of involvement of the vertebral arch, spinal cord, meninges and overlying dermis [23]. The spinal cord defect may present at any vertebral level with the most common being the lumbosacral region, which is associated with the final component of neural tube closure [20]. In addition to the structural abnormality, various other neurological defects may be present in the patient. These include hydrocephalus, diastematomyelia, Arnold-Chiari malformation, hydromyelia or

a tethered spinal cord [20]. Other signs of abnormalities may involve muscular balance, changes in bladder and bowel habits, sensory loss in the lower extremities and possibly paraplegia [23]. In addition, many patients present with dislocation of the hips, clubfeet, scoliosis or kyphosis. A classification system has been established to better characterize the types and severity of the spina bifida.

Spina bifida occulta

Spina bifida occulta results from the failure of fusion or development of part of the vertebral arch, usually lamina, which does not involve the spinal cord or meninges. Several studies report an incidence of approximately 10% to 24% in the population [24]. The studies state that this defect is usually asymptomatic, with only a small number of children showing concomitant defects in the spinal cord. Children with this defect usually present with a skin indentation and a patch of hair growing in the area of the lesion [20]. However, because this defect may not present with an external manifestation, X-ray examination is the only valid test to confirm this type of neural tube defect [23]. If the patient shows no associated abnormalities, no further treatment is necessary.

Spina bifida cystica

Spina bifida cystica is considered to be a severe defect, because it may involve the meninges as well as the spinal cord. Thus, several named subclasses of this defect exist. When the cyst involves the meninges and cerebrospinal fluid, it is referred to as spina bifida with meningocele. When the cyst also contains the spinal cord, the defect is referred to as spina bifida with meningomyelocele [12].

Spina bifida with meningocele

Patients developing spina bifida with meningocele usually have a layer of normal epidermis covering the meninges. This lesion does not involve the spinal cord, and therefore these patients usually do not present with any neurological symptoms [23]. External manifestations that may indicate this type of neural tube defect include hair growth in the area of the lesion, lipomas, cysts or hemangiomas [25].

Spina bifida with meningomyelocele

Spina bifida with meningomyelocele is more common than spina bifida with meningocele. It is considered a more severe neural tube defect because of the involvement of the spinal cord and meninges [4]. This lesion may be covered by a thin layer of skin or by a membranous sac. Patients with this lesion exhibit typical neurological symptoms, such as limb paralysis as well as bladder and bowel incontinence and may also present with hip dislocations. Because this defect may involve just the nerve roots or the entire spinal cord, paralysis may be of the flaccid, spastic or mixed type [26]. Other associated abnormalities may include hydroceph-

alus, Arnold-Chiari malformations and severe forms of scoliosis, kyphosis or lordosis.

Myeloschisis

Myeloschisis is considered to be the most severe type of spina bifida. This defect occurs as a result of the neural tube not closing properly with the developed spinal cord being exposed to the external environment [16]. Small patches of hair grow around the defect. As with spina bifida with meningomyelocele, involvement of the spinal cord translates into the possibility of one or more of the aforementioned associated defects, in addition to severe infection.

Causes of neural tube defects are thought to be multifactorial in nature. According to several studies, genetic contributions appear to be negligible, but future studies may reveal the role of inheritance in neural tube defects [27]. A slightly elevated risk of neural tube defects exists in siblings, but the data for risk regarding other relatives have yet to be proven. More important to the etiology of this defect is the environment. Various environmental and demographic variables may be involved with predisposing a fetus to a neural tube defect. According to Mitchell's epidemiologic review [27], these variables include season, location, ethnicity, economic status and maternal age.

Folic acid has been linked to neural tube defects in several studies. It appears that proper intake of folic acid may contribute to the prevention of neural tube defects [28]. Several studies involving folic acid and other metabolites involved with folic acid metabolism have shown promising results regarding prophylaxis of neural tube defects. Timing is the most important factor determining the efficacy of supplementation [28,29]. Several studies indicate that a dose of 0.8 mg reduces the occurrence of neural tube defects, and a dose of 4 mg can reduce the recurrence of a neural tube defect [30,31]. A study by Friel [29] indicated that mothers giving birth to children with neural tube defects ate a diet low in fruits and vegetables, while maintaining an increased level of sweets and other processed foods.

Other evidence of folic acid involvement in neural tube defects comes from a study done by Eskes et al. [32], who observed hyperhomocysteinemia in women giving birth to children with neural tube defects. However, the elevated homocysteine levels have not been proven, except in avian embryos, to be the major cause of neural tube defects. Elevated homocysteine levels may be the result of poor supplementation of folic acid or a mutation of the 5,10-methylenetetrahydrofolate reductase genes. The role of folic acid in hyperhomocysteinemia is its ability to convert homocysteine into methionine [33]. Thus, Eskes et al. [32] propose the hypothesis that an elevated homocysteine level may be the primary factor responsible for the neural tube defect, and poor folic acid supplementation may initiate or exacerbate this elevated level.

A second hypothesis from Van Aerts et al. [34] suggests that lower levels of methionine may also contribute to neural tube defects. DNA and RNA synthesis require methionine [34]. Thus, it follows that with lower levels development of the fetus may be severely impaired.

Further investigation revealed the importance of the methyl groups derived from the conversion. These methyl groups are vital for the synthesis of proteins, carnitine, lipids and various other molecules [32]. Future knowledge about the etiology of these defects will be obtained through the use of a transgenic mouse model.

Harris and Juriloff [35] studied genetic landmarks in mice with failed neural tube closure. They identified approximately 40 mutations with corresponding human homology that may be responsible for a neural tube defect. The conclusion of the study suggests that despite discovering these loci, many more probably exist and their role in causing this defect is still uncertain.

Whether physical location contributes to a neural tube defect, or if the environment has some affect on nutrition, which would subsequently cause the defect, remains uncertain. However, one can say with certainty that this defect is multifactorial and that defining one single cause is not plausible at this time.

Congenital scoliosis

An abnormal vertebral development that results in a lateral curvature of the spine is classified as congenital scoliosis. This type of spinal deformity occurs through a failure of formation or a failure of segmentation [17]. However, combined defects are the most common in congenital scoliosis [36]. The type and region of the malformation determines severity of the scoliosis. In addition, a sagittal deformity can be involved, creating either a kyphoscoliosis or a lordoscoliosis [17]. As with the other congenital spinal abnormalities, the defects appear to be sporadic, and studies have suggested a multifactorial basis, involving genetic and environmental contributions. Moore [11] attributes the failure of formation to an embryological absence of one or more of the primary chondrification centers [11]. As a result of the failure of cleavage of a primary center, part of the vertebra or growth plate will be unable to form and subsequent normal growth on the contralateral side will create the lateral curvature. In the case of a hemivertebra causing the scoliosis, an extra rib is a common additional finding [13]. A defined cause for the absence of the chondrification center remains unclear.

According to Jaskwicz et al. [13], 64% of cases of congenital scoliosis involve the thoracic vertebrae, whereas 20% involve the thoracolumbar region. Eleven percent of the cases are seen in the lumbar region, with the remaining 5% in the lumbosacral region. Although unusual, congenital scoliosis does occur in the cervical or cervicothoracic regions as well [37].

The natural history of congenital scoliosis plays a vital role in the prognosis and treatment of the defect. McMaster [38] demonstrated that the majority of curves are progressive, whereas only 25% are nonprogressive. Curves involving the thoracic vertebrae show the poorest prognosis with the most severe anomaly being a unilateral unsegmented bar with a contralateral single or multiple hemivertebrae [39]. In addition, curves in the cervicothoracic and lumbosacral regions are severe because there is a diminished ability for compensation by the rest of the spine [17]. McMaster stated further that the poorest prognosis involves the thoracolumbar region with a curve greater than 50 degrees by age 2 years [38]. Lonstein [17] ranks the prognosis of vertebral abnormalities in order beginning with poorest: a unilateral unsegmented bar, double-convex hemivertebrae, a single free convex hemivertebra and block vertebrae. Defects that are more severe tend to progress and usually require treatment. The curves that are less severe may not progress and present a greater challenge to the physician treating the patient [23]. Observation over a period of time may be the best solution in these cases. In addition, most physicians agree that a general rule regarding congenital abnormalities is to monitor carefully significant curve progression.

More complicated situations may also arise in cases of congenital scoliosis. In the case of a bilateral hemivertebra, the spine may actually be balanced with little or no curve progression. Alternatively, a patient may have a double curve, which may both require fusion [17].

Various anomalies may be associated with congenital scoliosis. The genitourinary tract, cardiac system and the spinal cord are the most common areas for associated abnormalities in scoliosis. A study of 218 patients by Beals and Rolfe [14] indicates that 61% had an anomaly involving the VACTERL syndrome. Klippel-Feil syndrome, or congenital fusion of cervical vertebrae and Sprengle deformity, which is an elevated scapula caused by failure to properly descend embryologically, are commonly associated with congenital scoliosis.

Special consideration should be given to abnormalities associated with the spinal cord, because they may require surgical treatment as well. Patients may present with tethered spinal cords, diastematomyelia, diplomyelia and syringomyelia [13].

Congenital scoliosis presents a major challenge to the physician as a result of the possibility of a wide variety of primary and secondary abnormalities [40]. These abnormalities develop during fetal life, and thus treatment of these patients often necessitates numerous tests and thorough repetitive examination by the physician.

Congenital kyphosis

Congenital kyphosis refers to a deformity in the sagittal plane resulting in an excessive flexion of the affected area. Defects of this kind are classified as failures of formation,

segmentation or dislocation of the spine as a result of rotation [41]. As discussed previously, kyphosis with an associated scoliosis may be observed. The cause of this defect is also considered multifactorial in nature.

In congenital kyphosis, a formational defect involves a complete or partial lack of a vertebral body. Deformities that are considered the most progressive usually have much more severe anterior defects [36]. Dubousset [41] attributes the remaining stability of the spine to the development of the posterior elements. In addition, failures of formation may be classified by the location of the abnormality and the position of the spinal cord canal. These classifications are important to a physician treating a patient presenting with such an abnormality.

Dubousset [41] differentiates these types of formation defects by using three subclasses. Congenital kyphosis may involve a partial failure of formation of a vertebral element with a canal that is still properly aligned. On the other hand, the defect may be a partial failure of formation with a malaligned canal. This defect usually involves the posterior arch as well. Finally, there can be a complete failure of formation of a vertebral body. In this case, paraplegia is usually evident at birth and can be found for the most part in the lumbar spine [41]. An additional subclass is a mixture of these defects. Defects of formation usually involve one level but can involve multiple levels. Most defects of formation occur in the thoracic or thoracolumbar segments of the spine and can encompass two to eight levels [35]. As a result, the patient may present with a congenital spondylolisthesis resulting from instability of the spine. Most physicians agree that the most severe congenital kyphosis involves a failure of formation and a concomitant scoliotic curve.

Failures of segmentation typically encompass more than one level and usually present as an unsegmented bar. The defect can be symmetrical or can show prevalence laterally. In the latter case, the patient presents with a kyphoscoliosis. The kyphosis may have a sharp or smooth angle depending on normal growth of the posterior elements and the extent of the congenital abnormality.

Rotatory dislocation of the spine, as described in *The Pediatric Spine* [41], is an area of kyphosis found between two congenital scoliotic curves, both of which are lordotic and in opposite directions. The combination of these defects creates the high likelihood of neurological complications. Rotatory dislocation of the spine is usually found in the thoracic or thoracolumbar regions but can involve any vertebral segments [41].

Defects involving thoracic vertebral levels four to nine usually cause paraplegia. The collateral circulation of the upper thoracic area is markedly less than other vertebral areas. A defect in the thoracolumbar region shows fewer propensities for developing paraplegia. It is known that the most common cause of spinal cord compression is congenital kyphosis. The defects involved in congenital kyphosis can be diagnosed early and should be treated before the growth

spurt, which as a result of the abnormal growth patterns can also lead to paralysis [42].

Congenital lordosis

This defect is very uncommon and the least severe of the three abnormal curvatures discussed in this review. Defects of this kind create an abnormal extension of the spine. The only embryological defect associated with true congenital lordosis is a defect of segmentation posteriorly. However, there can be a simultaneous scoliosis creating a lordoscoliosis [36]. Winter et al. states that most patients with a congenital lordosis exhibit some element of scoliosis. The cause of this defect is multifactorial in nature.

Dubousset [41] identifies three factors that may contribute to congenital lordosis. The first factor mentioned is the posterior defect of segmentation with concomitant normal anterior development. The second factor involves abnormal or lack of formation of the posterior elements. Spinal dysraphisms with defects in the posterior elements can be a primary cause of congenital lordosis. Finally, congenital lordosis may be a compensatory deformity as a result of a kyphosis at a lower vertebral level.

As with other congenital vertebral defects, various systems may be involved. In the cardiopulmonary system, a severe lordosis can cause both constriction and stretching of the bronchi leading to atelectasis [41]. These patients will present with severe pulmonary distress. In addition, typical abnormalities of the genitourinary and cardiac systems may be present in these patients. Patients with congenital lordosis also present with nervous system malformations. This condition is considered rare, but because of associated secondary abnormalities, it may develop into a severe defect when left untreated.

Klippel-Feil syndrome

Klippel-Feil syndrome or *brevicollis* involves the congenital fusion of two or more cervical vertebrae. Maurice Klippel and his resident Andre Feil were the first orthopedists to describe the syndrome. This abnormality is the result of a failure of proper segmentation of vertebrae in the cervical region during embryonic development. In addition, theories suggest that defects in the notochord and notochord signaling may also cause this syndrome [5]. Patients presenting with this defect have congenitally fused cervical vertebrae causing a shortened neck with a low posterior neckline and a diminished ability to move in the affected area [43]. Patel and Lauerman [44] reports that all three of the aforementioned symptoms can be found in 50% of the patients diagnosed with Klippel-Feil. Patients are restricted to flexion and extension between the occiput and atlas.

Klippel-Feil syndrome is classified into three categories: Type I, II and III. In Type I, the patient presents with numerous fused cervical vertebrae and possibly upper thoracic

vertebrae with synostosis. Type II includes fusion of one or two vertebrae and other abnormalities of the cervical spine. Type III includes fusion of cervical vertebrae with concomitant fusion of thoracic or lumbar vertebrae [45]. A fourth type addresses genetic heterogeneity and affected levels in the cervical spine [46].

Although a higher incidence exists in females, there has been little supporting evidence to suggest an existing pattern of inheritance. This defect is seen in approximately 1 in 42,000 births. As with most congenital defects, O’Rahilly [1] supports the theory of a multifactorial etiology. A study on 50 patients by Hensinger et al. [47] shows that there are a variety of associated abnormalities with Klippel-Feil syndrome. The study also stresses that the associated defects may be more detrimental to the patient than problems associated with the clinical description listed above. Sixty percent of patients with this syndrome have scoliosis, and 35% have an abnormality in the urinary system. The degree of scoliosis is most severe in Type I Klippel-Feil and decreases in severity in Type III and Type II, respectively [45]. In addition, 30% of patients present with impaired hearing. Other associated anomalies include Sprengle deformity, cardiovascular disease and synkinesia [43]. Patel and Lauerman [44] underscores the possibility of an associated spina bifida, web neck and brainstem malformation. A study by Hall et al. [48] lists 38 anomalies that may be associated with Klippel-Feil Type I, II or III. The greatest number of anomalies is associated with Type I and Type II.

Hall et al. [48] explains in a case report the possible neurological consequences of Klippel-Feil syndrome. The patient may present with radiculopathy, myelopathy or quadriplegia. These findings may be attributed to spondylosis of

the cervical spine or instability of vertebrae adjacent to the fused segment, both of which can compress the spinal cord or spinal nerves.

Patients with Klippel-Feil can present with an array of symptoms and may not present with the classic findings. However, it is important for the physician to recognize the syndrome in order to address the issue of cervical stability, any degenerative changes that may occur in lower cervical segments and other associated abnormalities [46].

Congenital spondylolisthesis

Spondylolisthesis is a condition that involves a forward slip of a vertebra or vertebrae in relation to the rest of the spinal column. Herbiniaux first described the condition in 1782 as a protruding sacral bone that complicated labor. Typically, this defect occurs between the fifth lumbar vertebra and the sacrum [43]. However, spondylolisthesis has also been seen between the fourth and fifth lumbar vertebral levels and may even occur in the cervical region. Tokgozoglu and Alpaslan [49] discuss two cases of congenital spondylolisthesis in the cervical and thoracic regions. The patients showed deficits in their neurological examinations and required stabilization and fusion. Studies showing an increase among family members with this defect suggest a genetic component.

There are various types of spondylolisthesis. Thus, a classification system was established to differentiate the specific etiologies. This review limits its discussion to congenital spondylolisthesis, which is a Newman Type I defect. The cause of congenital or dysplastic spondylolisthesis, which is most commonly found at the lumbosacral junction, occurs

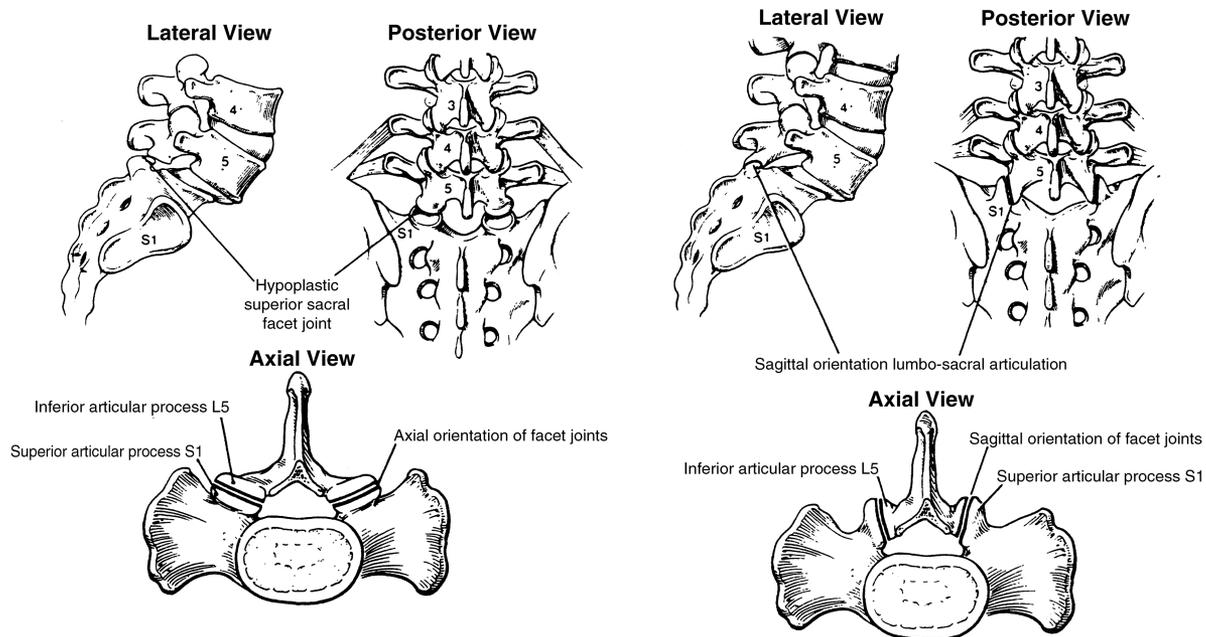


Fig. 9. Congenital spondylolisthesis from facet joint dysplasia. (Reprinted from Frymoyer JW, Ducker TB, Hadler NM, et al., eds. *The adult spine: principles and practice*, vol. 2., 1991, with permission from Lippincott Williams & Wilkins.)

as a result of an elongation of the pars interarticularis along with varying degrees of facet joint dysplasia (Fig. 9) [50]. Wynne-Davies and Scott [51] reported an increased incidence for neurological symptoms when the slippage exceeds 35%, assuming the bony elements are intact. Patients may present with back pain, radicular complaints, tight hamstrings and various neurological symptoms [52]. The possibility of developing impairment of bowel and bladder function exists with high-grade neural compression. Neurological deficits necessitate prompt surgical intervention [53].

Conclusion

Development of the spine occurs through a complex series of events involving genes, signaling pathways and various metabolic processes. This review has focused on numerous common abnormalities that may be associated with these processes. In addition, because several systems develop from a common precursor, a defect early in fetal life may have a variety of clinical presentations. Physicians should be aware of these common types of congenital spinal defects as well as have an understanding of the normal embryologic process of development. Recognition of any of these defects indicates the need for a thorough physical examination to identify possible associated abnormalities in other systems as well.

References

- [1] O’Rahilly R. Human embryology and teratology. New York: John Wiley & Sons, 1996.
- [2] Slack JMW. We have a morphogen!. *Nature* 1987;327:553–4.
- [3] Tabin CJ. Retinoids, homeoboxes, and growth factors: toward molecular models for limb development. *Cell* 1991;66:199–217.
- [4] Moore K, Persaud TVN. The developing human: clinically oriented embryology, 6th ed. Philadelphia: W.B. Saunders Company, 1998.
- [5] Nolting D, Hansen B, Keeling J, Kjaer I. Prenatal development of the normal human vertebral corpora in different segments of the spine. *Spine* 1998;23(21):2265–71.
- [6] Capecchi MR. Function of homeobox genes in skeletal development. *Ann NY Acad Sci* 1996;785:34–7.
- [7] Gasser RF. Evidence that sclerotomal cells do not migrate medially during normal embryonic development of the rat. *Am J Anat* 1979;154:509–24.
- [8] Wilting J, Muller TS, Ebensperger C, et al. Development of the vertebral column: morphogenesis and genes. In: Vogel R, Fanghaenel J, Giebel J, eds. Aspects of terminology. Marburg, Germany: Tectum Verlag, 1996.
- [9] Wilting J, Kurz H, Brand-Saberi B. Kinetics and differentiation of somite cells forming the vertebral column: studies on human and chick embryos. *Anat Embryol* 1994;190:573–81.
- [10] Trout J, Buckwalter JA, Moore KC, Landas SK. Ultrastructure of the human intervertebral disc. *Tissue Cell* 1982;14:359–69.
- [11] Moore K. Back. In: Kelly P, ed. Clinically oriented anatomy. New York: Lippincott Williams & Wilkins, 1999. p. 432–99.
- [12] Weston JA. Regulation of neural crest cell migration and differentiation. In: Gerhart J, ed. Cell interactions and development. New York: John Wiley & Sons, 1982. p. 150–70.
- [13] Jaskwhich D, Ali RM, Patel TC, Green DW. Congenital scoliosis. *Curr Opin Pediatr* 2000;12(1):61–6.
- [14] Beals R, Rolfe B. Current concepts review VATER association: a unifying concept of multiple anomalies. *J Bone Joint Surg Am* 1989;71:948–50.
- [15] MacEwen GD, Winter RB, Hardy JH. Evaluation of kidney anomalies in congenital scoliosis. *J Bone Joint Surg Am* 1972;54:1451–4.
- [16] Lonstein JE, Winter RB, Moe JG, Bradford DS, Chou SN, Pinto W. Neurologic deficits secondary to spinal deformity: a review of the literature and report of 43 cases. *Spine* 1980;5:331–5.
- [17] Lonstein JE. Congenital spine deformities: scoliosis, kyphosis, and lordosis. *Orthop Clin North Am* 1999;30(3):387–405.
- [18] Csaboy L, Szabo I, Papp C, Toth-Pal E, Papp Z. Central nervous system anomalies. *Ann NY Acad Sci* 1998;847:21–45.
- [19] Murphy M, Seagroatt V, Hey K. Neural tube defects 1974–1994—down but not out. *Arch Dis Child* 1996;75:F133–4.
- [20] Bendo J, Spivak J, Cally D, Letko L. Orthopaedics: a study guide. New York: McGraw-Hill, 1999.
- [21] Ghidini A, Siclerer S, Willmer J. Congenital abnormalities (Vater) in baby born to mother using lovastatin. *Lancet* 1992;339(8806):1416–7.
- [22] Nora JJ, Nora AH, Blu J, et al. Exogenous progesterone and estrogen implicated in birth defects. *JAMA* 1978;240(8):8737–43.
- [23] Keim H. The adolescent spine. New York: Grune & Stratton, 1982.
- [24] Williams PL, Bannister LH, Berry MM, et al. Gray’s anatomy. New York: Churchill Livingstone, 1995.
- [25] Drolet BA. Cutaneous signs of neural tube dysraphism. *Pediatr Clin North Am* 2000;47(4):813–23.
- [26] Rintoul NE. A new look at myelomeningoceles: functional level, vertebral level, shunting, and the implications for fetal intervention. *Pediatrics* 2002;109(3):409–13.
- [27] Mitchell L. Genetic epidemiology of birth defects: nonsyndromic cleft lip and neural tube defects. *Epidemiol Rev* 1997;19(1):61–8.
- [28] Lewis D, Van Dyke D, Stumbo P, Berg M. Drug and environmental factors associated with adverse pregnancy outcomes part II: improvement with folic acid. *Ann Pharmacother* 1998;32:947–60.
- [29] Friel JK, Frecker M, Fraser FC. Nutritional patterns of mothers of children with neural tube defects in Newfoundland. *Am J Med Genet* 1995;55:195–9.
- [30] Seller MJ, Nevin NC. Periconceptional vitamin supplementation and the prevention of neural tube defects in South-East England and Northern Ireland. *J Med Genetics* 1984;21:325–30.
- [31] Iqbal MM. Prevention of neural tube defects by periconceptional use of folic acid. *Pediatr Rev* 2000;21(2):58–66.
- [32] Eskes TKAB. Open or closed? A world of difference: a history of homocysteine research. *Nutr Rev* 1998;56(8):236–44.
- [33] Finkelstein JD. Methionine metabolism in mammals. *J Nutr* 1990;1:228–37.
- [34] Van Aerts LAGJM, Blom HJ, Deabreu RA, et al. Prevention of neural tube defects by and toxicity of L-homocysteine in cultured postimplantation rat embryos. *Teratology* 1994;50:348–60.
- [35] Harris MJ, Juriloff DM. Genetic landmarks for defects in mouse neural tube closure. *Teratology* 1997;56:177–87.
- [36] Winter RB, Lonstein JE, Boachie-Adjei O. Congenital spinal deformity. Instructional Course Lectures 1996;45:117–27.
- [37] Smith MD. Congenital scoliosis of the cervical or cervicothoracic spine. *Orthop Clin North Am* 1994;25(2):301–10.
- [38] McMaster MJ. Congenital scoliosis. In: Weinstein SL, ed. The pediatric spine: principles and practice. New York: Raven Press, 1994. p. 2255–9.
- [39] McMaster MJ. Congenital scoliosis caused by a unilateral failure of segmentation with contralateral hemivertebrae. *Spine* 1998;23:998–1005.
- [40] Day G, Upadhyay S, Ho E, Leong J, Ip M. Pulmonary function in congenital scoliosis. *Spine* 1994;19:1027–31.
- [41] Dubouset J. Congenital kyphosis and lordosis. In: Weinstein SL, ed. The pediatric spine: principles and practice. New York: Raven Press, 1994. p. 2183–7.

- [42] Kim Y. Surgical treatment of congenital kyphosis. *Spine* 2001; 26(20):2251–7.
- [43] An H. Synopsis of spine surgery. Baltimore: Williams & Wilkins, 1997.
- [44] Patel R, Lauerma W. Historical perspective: Maurice Klippel. *Spine* 1995;20:2157–60.
- [45] Thomsen M, Schneider U, Weber M, Johannisson R, Niethard F. Scoliosis and congenital anomalies associated with Klippel-Feil syndrome Types I–III. *Spine* 1997;22(4):396–401.
- [46] Pizzutillo P, Woods M, Nicholson L, MacEwen G. Risk factors in Klippel-Feil syndrome. *Spine* 1994;19(18):2110–6.
- [47] Hensinger R, Lang J, MacEwen G. Klippel-Feil syndrome. A constellation of associated anomalies. *J Bone Joint Surg* 1974;56A:1246–53.
- [48] Hall J, Simmons E, Danylchuk K, Barnes P. Instability of the cervical spine and neurological involvement in Klippel-Feil syndrome. *J Bone Joint Surg (Am)* 1990;72(3):460–2.
- [49] Tokgozoglu A, Alpaslan A. Congenital spondylolisthesis in the upper spinal column: management of two cases. *Spine* 1994;19(1):99–102.
- [50] Armstrong G, Ye B. Sacral configuration in dysplastic spondylolisthesis. *J Bone Joint Surg (Br)* 1985;67:335–40.
- [51] Wynne-Davies R, Scott J. Inheritance and spondylolisthesis. A radiographic family survey. *J Bone Joint Surg (Br)* 1973;61:301–5.
- [52] Bradford D, Hu S. Spondylolysis and spondylolisthesis. In: Weinstein SL, ed. *The pediatric spine: principles and practice*. New York: Raven Press, 1994. p. 2640–50.
- [53] Grobler L, Wiltse L. Classification and nonoperative and operative treatments of spondylolisthesis. In: Frymoyer JW, Ducker TB, Hadler WM, eds. *The adult spine: principles and practice*, vol. 2. Philadelphia: Lippincott Williams & Wilkins, 1991. p. 1865–922.



Forty Years Ago in Spine

In 1965, Williams [1] published a text that emphasized nonoperative care of lumbar pain. The

text contained his description of an exercise regimen that came to be known as “Williams’ flexion exercises,” which were the dominant form of exercise for low back pain, until challenged by Robin McKenzie [2] and others.

References

- [1] Williams PC. *The lumbosacral spine, emphasizing conservative management*. New York: Blakiston, 1965:80–93.
- [2] McKenzie RA. *The lumbar spine: mechanical diagnosis and therapy*. Waikanae, New Zealand: Spinal Publications, 1981.