ONGENITAL kyphosis has been classified into three groups: Type I (defect of development); Type II (defect of segmentation); and Type III (defect of development and segmentation). Until recently little was known about the molecular mechanisms of normal vertebral morphogenesis and, therefore, our understanding of abnormal vertebral development and segmentation was incomplete. Increasing knowledge of the role of developmental control genes in the genesis of the vertebral column may offer an embryological basis for extensive vertebral anomalies.

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**Case Report**

This 50-year-old Egyptian man presented with a 1-year history of gradually increasing leg stiffness that progressed to spastic paraparesis.

*History.* He had suffered from progressive kyphoscoliosis since the age of 2 years. At that time he was treated for 1 year with a plaster jacket that was changed regularly. He enjoyed a normal life, acquiring three university degrees and was able to run until 1 year before his admission. He had a history of nephrolithiasis, for which he underwent open pyelolithotomy and lithotripsy, and no history of tuberculosis or other infection affecting the spine. His mother had suffered from rheumatoid arthritis since her early 50s but his family history was otherwise unremarkable.

*Examination.* The patient was dysmorphic, with a short and kyphotic trunk and normal-sized head, neck, and limbs. He was unable to walk more than a few yards for which he required the help of a cane. The general physical and laboratory examinations were normal except that the patient had reduced ventilatory capacity. Neurological examination revealed a grade 4-5 spastic paraparesis with upgoing plantar reflexes and hypesthesia below the waist with preservation of joint position sense.

*Radiological Findings.* An anteroposterior roentgenogram, after intrathecal administration of contrast material, showed a block of the contrast medium in the thoracolumbar region and a crablike appearance of the thoracic cage with 12 pairs of ribs (Fig. 1). Magnetic resonance imaging confirmed severe spinal cord compression at this level and clearly showed seven cervical, six thoracic, and two lumbar vertebrae, all with reduced anteroposterior diameter. The fifth and sixth thoracic vertebral bodies were “fused” (Fig. 2). There was a large osseous mass forming the anterior part of the kyphos at the thoracolumbar junction that faintly showed four segments on coronally reformatted computerized tomography scan (Fig. 3).

**Inadequate PAX-1 gene expression as a cause of agenesis of the thoracolumbar spine with failure of segmentation**

**Case report**

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An unusual case with absence and “fusion” of several thoracic and lumbar vertebral bodies leading to a severe thoracolumbar kyphos is presented. Late-onset neurological deterioration occurred due to spinal cord compression, which was treated with anterior decompression. Although several mechanisms for the development of these extensive and rare abnormalities have been proposed, the cause in humans remains unknown. An embryological basis is presented in the light of recent advances in molecular genetics, which show that abnormal notochordal signals and Pax-1 gene expression can produce an experimental phenotype very similar to the one in the patient described here. Thus it is suggested that faults in these early developmental processes may be, at least in part, responsible for the development of such extensive anomalies.

**KEY WORDS** • congenital anomaly • kyphoscoliosis • vertebral anomaly • notochord • Pax-1 gene • segmentation

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Operation. The patient was placed in the right lateral decubitus position and the kyphos was approached retropleurally through a left T8–11 costotransversectomy. The dura was decompressed by drilling out and removing the apex of the kyphos. A large iliac crest strut graft was placed behind the still intact and rigid anterior border of the partially excised thoracolumbar kyphos. Effective internal fixation with metal implants was not possible because of the severe deformity of the spine. The excised bone fragments showed no bacterial growth on culture or signs of abnormal ossification on histological analysis.

Postoperative Course. The patient made an uncomplicated recovery. He was mobilized in a specially made stiff body jacket and started to walk with two canes. He was discharged 2 weeks after the procedure.

Discussion

Progressive kyphoscoliosis may be congenital or secondary to spinal infection, trauma, neuromuscular disorders, vertebral anomalies, or surgery. The early onset of the disease in the absence of other relevant medical history and the appearance of the normal vertebral bodies with reduced anteroposterior diameter and preservation of vertebral height and width suggest a congenital origin of the extensive anomalies that lead to a marked degree of late neurological deterioration in this patient. Although it is unusual for neurological impairment to occur late in life, this is not the first patient to present in the sixth decade.12

Developmental Background

In the 4th week of embryonic development the definitive notochord is already formed from the primitive node, and the first somites (paired segmental units of epithelial paraxial mesoderm) appear at the cephalic end of the three-layered embryonic disc. From the somites three paired primordia arise: dermatome, myotome, and sclerotome. Signaling from the notochord and the neural tube orchestrate the formation of the vertebral column from the somites. Mesodermal cells from the ventromedial part of the sclerotomes spread out and surround the notochord. A clear distinction must be made between this centrally placed material that surrounds the notochord and the laterally placed sclerotomes. Hence a distinction has to be made between lateral and axial (central) development of the vertebrae. Laterally, each sclerotome differentiates into a loosely cellular cranial and a densely cellular caudal half. The dorsal part of each caudal sclerotome half gradually surrounds the neural tube and eventually develops into the posterior vertebral elements (pedicle, costal process, lamina, and spinous process). Axially, the cellular perichordal sheath subsequently becomes segmented with alternating loosely and densely populated cellular areas. The loose areas develop into vertebral centra (which will form the vertebral bodies), separated by densely cellular areas (anlagen for the intervertebral discs).4,5,9

![Fig. 1. Anteroposterior spinal myelogram. The column of contrast medium stops at the thoracolumbar junction. The thoracic cage shows a crablike appearance, with 12 pairs of ribs. The kyphos is shown between the T-6 and L-3 levels (large arrows). A faint space between the incompletely separated fifth and sixth thoracic vertebral bodies is shown (small arrow).](image1)

![Fig. 2. A T2-weighted sagittal magnetic resonance image revealing only six thoracic and two lumbar vertebrae with normal height but reduced anteroposterior diameter. The T-5 and T-6 vertebrae are not separated and a large osseous mass, forming the anterior part of the kyphos, is visible. The second and seventh cervical vertebrae are shown (C2 and C7), and so are the kyphos (K) and the body of the fifth lumbar vertebra (L5).](image2)
The process of segmentation is not fully understood; nevertheless, significant advance has been made in recent years with the discovery of some developmental control genes. Common to all these genes are phylogenetically highly conserved DNA sequences termed “homeobox” (Hox genes) and “paired box” sequences (Pax genes). So far nine human Pax genes have been characterized. They encode proteins that modulate morphogenesis by influencing the transcription of specific downstream genes. It has been shown in mice and chick embryos that the Pax-1 gene plays an early role in sclerotome patterning and in the development of the perichordal sheath and a late function by influencing the development of intervertebral discs during vertebral chondrification. Signals from the notochord and/or the floor plate of the neural tube are necessary for normal Pax-1 expression; abnormalities in notochord signals result in reduced Pax-1 gene expression. This reduced expression leads to a reduction in the number of vertebral bodies and rib heads with preservation of the laminae. Smith and Tuan used antisense methodologies in chick embryos to investigate whether abnormal expression of the Pax-1 gene during somite development causes an abnormal phenotype. Inactivation of Pax-1 gene expression, in their experiments, resulted in complete loss and/or “fusion” of somites. This would then result in total absence of vertebral bodies with extensive “fusions,” very similar to our presented case (Fig. 4).

Our patient is an extreme example of a Type III congenital kyphosis and falls into the group of extensive coalition anomalies of the thoracic vertebrae. However, this patient not only had severe kyphosis but, even taking into account the segments within the kyphos, he also lacked at least five vertebral bodies. The cause for this anomaly remains obscure. Anomalous segmental vascular supply, osseous metaplasia, mechanical imbalance, cell dispersion, and defective mesodermal development, among others, have been proposed to explain the origin of such extensive vertebral anomalies.
tioned molecular genetic findings suggest, however, that an early defect of the notochord and/or perturbation of PAX-1 gene expression may indeed play a role in the development of severe failures of axial segmentation and total absence of vertebral segments, both observed in the present case.

References


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