Case Report

Pediatric Neurosurgery

Pediatr Neurosurg 1999;30:272–277

Received: February 8, 1999
Accepted: April 16, 1999

Segmental Costovertebral Malformations: Association with Neural Tube Defects

Report of 3 Cases and Review of the Literature

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Key Words

Jarcho-Levin syndrome · Neural tube defect · Polythelia · Tethered cord · Spondylocostal dysostosis

Abstract

Patients with spondylocostal dysostosis (SCD) have vertebral abnormalities and numerical or structural rib anomalies that produce thoracic asymmetry. Rib anomalies and dysmorphism are the typical features that differentiate this syndrome from spondylothoracic dysostosis (STD). Jarcho-Levin syndrome is a severe form with involvement of the whole vertebral column. Other associated findings such as congenital heart defects, abdominal wall malformations, genitourinary malformations and upper limb anomalies may be found; in addition, neural tube defects (NTDs) have been associated with this malformation. SCD is transmitted both in a recessive form and as a dominant defect. We report on 3 children with SCD; 2 also had NTDs. All of them were studied with X-rays and spinal magnetic resonance (MR), and over the same period they underwent multidisciplinary clinical functional evaluation. One of our cases with NTD also presented polythelia, which has not previously been described in patients with SCD. The common association of segmental costovertebral malformations with NTDs could be related to an early gastrulation genomic defect, or one after gastrulation, when there are two independent somitic columns. The latter sometimes progresses and then involves primary and secondary neurulation. Also, the association of SCD with NTDs could be related to the interaction of different genes, resulting in this complex phenotype. Therefore, additional genetical and embryological studies are necessary to provide evidence of an etiological link between SCD and NTD.

Spondylocostal dysostosis (SCD) is a congenital disorder with multiple vertebra and numerical or structural rib abnormalities resulting in thoracic asymmetry and short stature and neck [1, 2]. Spondylothoracic dysostosis (STD) involves the spine and leads to a fanlike chest, but no intrinsic rib malformation [3]. Jarcho-Levin syndrome is a severe form with involvement of the whole vertebral column [1–5]. SCD is transmitted both in a severe recessive form and as a dominant defect [2]. The common association of rare segmental costovertebral malformations and neural tube defects (NTDs) suggests an etiological link [1, 4–11]. The various associated clinical anomalies derived from three germ layers in NTDs are listed in table 1.

We describe 3 patients with SCD; 2 patients also had NTDs. One of our cases with SCD and NTD also presented polythelia, which has not previously been described in patients with SCD.

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1016–2291/99/0305–0272$17.50/0

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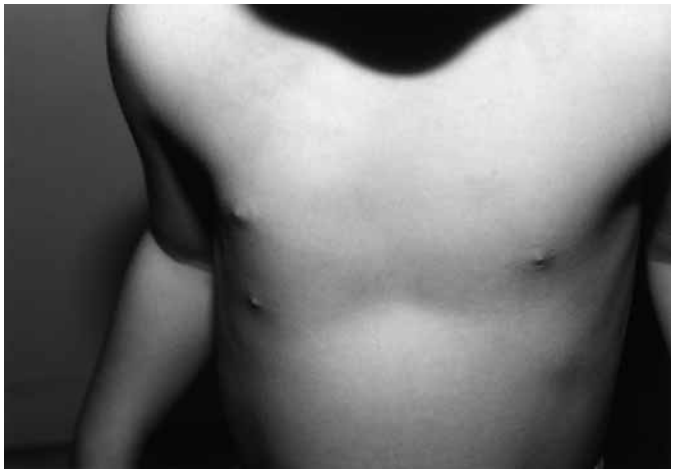
Table 1. Clinical anomalies or/and syndromes associated with NTDs

Brain anomalies	microgyria polygyria enlargement of the massa intermedia agenesis or dysgenesis of the corpus callosum cerebellar dysgenesis Arnold Chiari malformation type II (including hydrocephalus and other specific anomalies due to this malformation)
Ventricular anomalies	aqueductal stenosis, forking and atresia third ventricle atresia fourth ventricle stenosis
Brain stem anomalies	hypoplasia or aplasia of cranial nerve nuclei, olives, basal pontine nuclei, tegmentum defective myelinization
Spinal cord anomalies	hydromyelia split cord anomalies defective myelinization
Vertebra anomalies	absence of the spinous processes and laminae or rudimentary laminae reduction in the anteroposterior size of the vertebral body increase in the interpedicular distance decreased height of the pedicle laterally extended large transverse processes hemivertebrae, fused vertebrae, sagitally clefted (butterfly) vertebrae, missing vertebrae, midline osseous or fibrocartilaginous spurs (as is seen in STD and Jarcho-Levin syndrome)
Rib anomalies	fused or missing ribs (as is seen in spondylocostal dysostosis)
Systemic anomalies	gastrointestinal: inguinal hernia, Meckel's diverticulum omphalocele, imperforate anus, neurenteric cysts pulmonary: pulmonary agenesis/hypoplasia cardiovascular: ventricular or atrial septal defects, patent ductus and coarctation of the aorta genitourinary: renal agenesis and hypoplasia, horseshoe kidney, bladder duplications, genital duplications (the commonest) craniofacial anomalies cutaneous malformation: hemangiomata, hypertrichosis, polythelia (in our case)

Case Reports

Case 1

A 2-year-old girl was admitted to hospital with lipomyelomeningocele. The child's parents are nonconsanguineous. This lesion was fully skin covered with a soft and nontender lumbosacral mass in the midline. On admission, physical examination revealed a short neck, thoracic asymmetry and also polythelia on the right side (fig. 1). She also has bilateral foot deformities.



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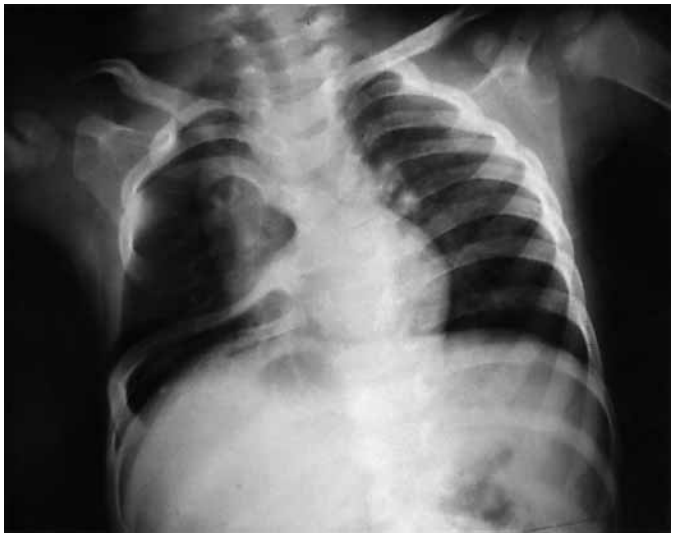

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Fig. 1. Polythelia on the right side in case 1.
Fig. 2. Anteroposterior radiograph showing hemivertebrae, sagitally clefted vertebra (butterfly) and missing ribs corresponding to missing vertebrae on that side in case 1.

Neurological examination revealed muscle weakness of the lower extremities, particularly the distal extremities. She could not begin to walk. Thoracic X-ray showed costovertebral abnormality with T_3 sagitally clefted vertebra (butterfly), T_4 and T_5 hemivertebrae, and missing 4th and 5th rib anomaly (fig. 2). The missing ribs corresponded to the missing vertebrae on that side. Lumbosacral X-ray also showed widening of the spinal canal with posterior fusion defect at the level of the lipomyelomeningocele (fig. 3). There were no anomalies of other organ systems. Midsagittal spinal magnetic resonance imaging (MRI) revealed the large subcutaneous lipoma extending through a fascial, bony and dural defect into a caudally descending and dorsally situated spinal cord (fig. 4a). Axial MRI showed the dorsal location of the lipoma (fig. 4b). There were no malformations of the spine other than the lipoma on complete spinal MRI.

The patient underwent multidisciplinary clinical and functional evaluation. Urodynamic testing showed a hypertonic bladder. At

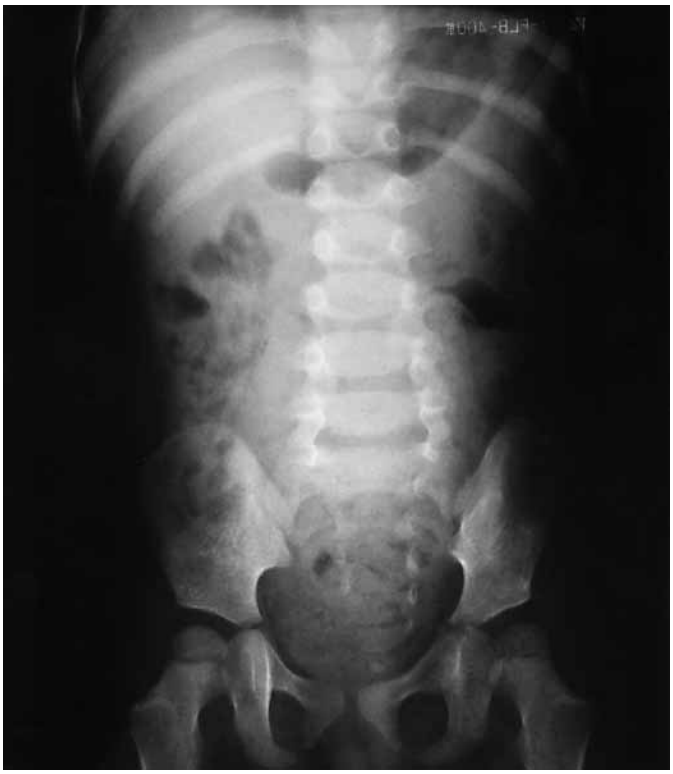


Fig. 3. Lumbosacral radiograph showing widening of the spinal canal with posterior fusion defect at the level of the lipomyelomeningocele in case 1.

operation, a lipomatous mass was trimmed subpially, and after excision of the lipoma, the conus was detethered and the dural sac was reconstructed by using a Gore-Tex (W.L. Gore & Associates, Inc., Flagstaff, Ariz., USA) surgical membrane.

The patient had no additional neurological deficits during the postoperative period. Orthopedic operations were performed for the foot deformities. Six months later, she was able to walk without a helper. She underwent multidisciplinary clinical and functional follow-up.

Case 2

A 6-month-old girl was admitted to hospital with shunt infection and urinary problems. The child's parents are nonconsanguineous. She had undergone repair of a myelomeningocele and placement of a ventriculoperitoneal shunt in another hospital. On physical examination, she had hydrocephalus, minimal thorax deformity, thoracolumbar kyphosis and thoracolumbar midline scar tissue due to myelomeningocele repair. X-ray of the thorax and spine showed T_5 and T_6 hemivertebrae, missing 5th and 6th rib anomaly (fig. 5a) and severe thoracolumbar kyphosis (fig. 5b). The missing ribs corresponded to the missing vertebrae on that side. There were no malformations of the spine other than the myelomeningocele on preoperative complete spinal MRI. Ultrasonography demonstrated bilateral hydronephrosis. After the treatment of cerebrospinal fluid and urinary infection, she underwent shunt revision followed by multidisciplinary clinical and functional follow-up.

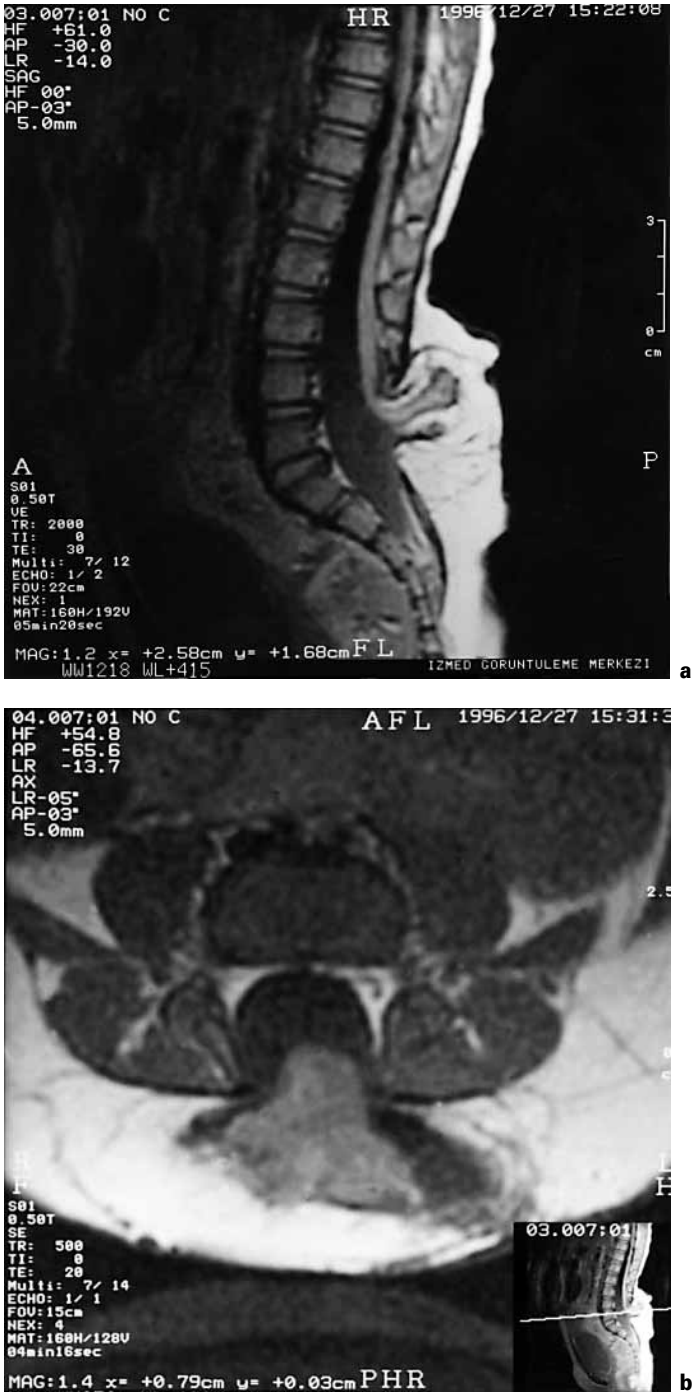
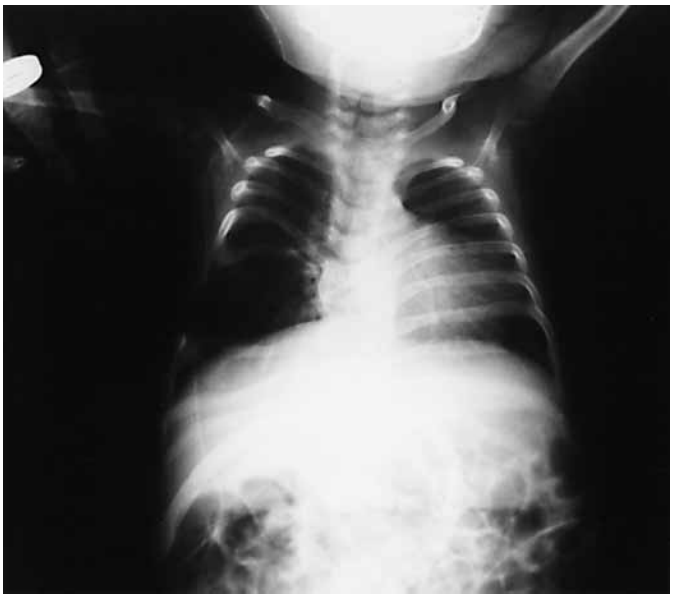


Fig. 4. a Midsagittal spinal MR revealing the large subcutaneous lipoma extending through a fascial, bony and dural defect into the caudally descending and dorsally situated spinal cord in case 1. **b** Axial spinal MR showing the dorsal location of the lipoma in case 1.



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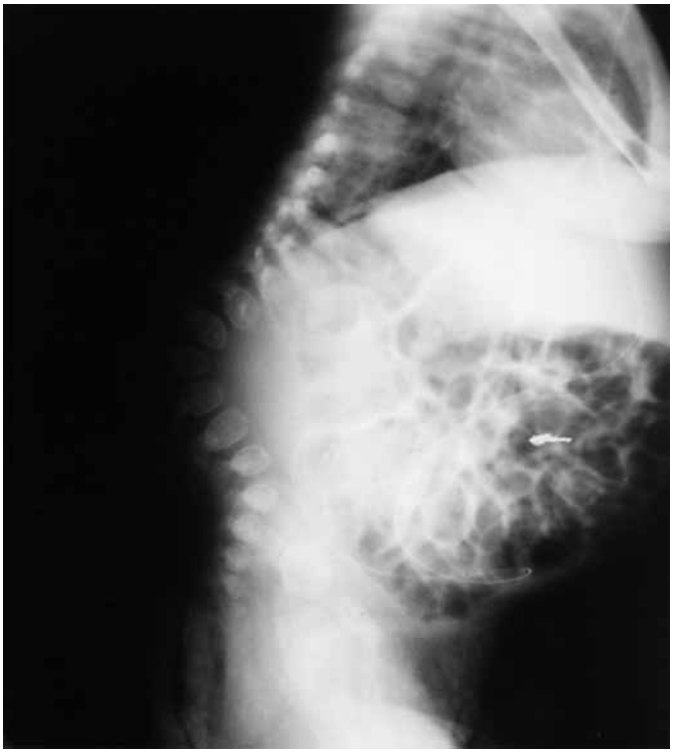

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Fig. 5. a Thorax X-ray showing rib abnormalities in case 2. **b** Lateral radiograph showing thoracolumbar kyphosis in case 2.

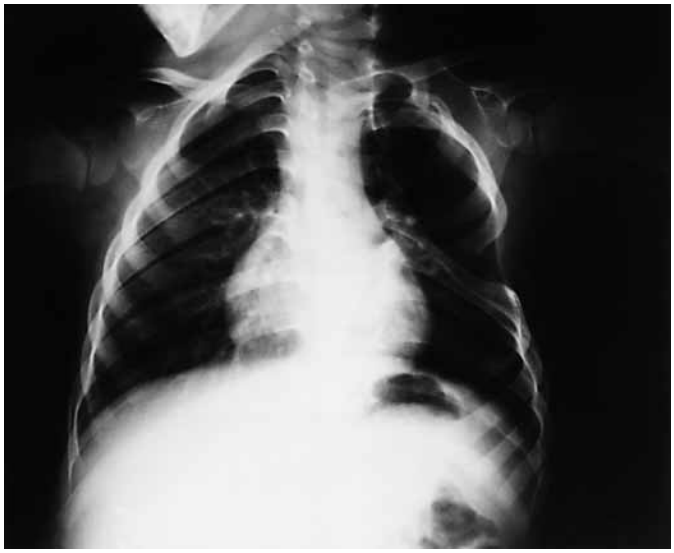

Fig. 6. Thorax X-ray showing butterfly vertebrae, hemivertebrae and rib abnormalities in case 3.

Case 3

A 1-year-old girl was admitted to hospital with only asymmetry of the thorax. The child's parents are nonconsanguineous. Physical examination was unremarkable except for thorax deformity. Neurological examination was normal. Thoracic X-ray showed vertebral abnormality with T_4, T_5 hemivertebrae, T_3 sagitally clefted vertebra (butterfly) and missing 4th and 5th rib anomaly (fig. 6). Lumbosacral X-ray and complete spinal MRI were normal. She underwent multidisciplinary clinical and functional follow-up without any intervention.

Discussion

In 1975, Wynne-Davies [11] reported that sibs of patients with localized multiple vertebral anomalies had an increased incidence of anencephaly or spina bifida cystica compared to the incidence in the general population. In 1976, McLennan [7] reported that vertebral anomalies were found concomitantly with abnormal ribs in about half the patients with spina bifida. In 1978, Naik et al. [8] made a radiological necropsy study of vertebral and rib malformations in children with myelomeningocele. They demonstrated that 64 had various anomalies, including fused vertebral arches, fused vertebral bodies, absence of vertebral bodies and absent or fused ribs [8]. Poor et al. [9] described a case of Jarcho-Levin syndrome associated with cerebral polygyria. Reyes et al. [10] reported a case of Jarcho-Levin syndrome associated with diastematomyelia. These authors claim that neurological abnormalities should be con-

sidered a component of Jarcho-Levin syndrome [9, 10]. Giacoia and Say [1] reported a patient with Jarcho-Levin syndrome who also had spina bifida, diastematomyelia and hydrocephalus. They also described nonskeletal malformations such as cleft palate, triangular opening of the mouth, imperforate anus, undescended testes and dextroposition of the heart with atrial septal defect [1].

Jarcho-Levin syndrome, STD and SCD are rare and distinct entities which share similar clinical phenotypes [3]. Jarcho-Levin syndrome, which is transmitted in an autosomal recessive way, is a severe form with involvement of the whole vertebral column, and in most cases small size of the thorax; death from respiratory infection ensues from the thoracic anomalies [1–5]. STD is transmitted in an autosomal recessive way; it involves the spine and leads to a fanlike chest, but there is no intrinsic rib malformation [3]. Patients with SCD have vertebral abnormalities such as hemivertebrae, fused, hypoplastic, 'butterfly' vertebrae and characteristic rib anomalies [3]. SCD is transmitted both in a severe recessive form and as a dominant defect. Short neck, short trunk, as well as asymmetry of the thorax and abdomen bring these patients to medical attention [1]. Spina bifida occulta appears to be a common finding in reported SCD cases [9, 10, 12, 13].

Case 1 reported here is a patient with lipomyelomeningocele occurring in association with findings characteristic of SCD. There was no congenital heart defect, abdominal wall malformation, genitourinary malformation and upper limb anomalies in our case. However, this case also presented polythelia, not previously described in patients with SCD.

Mammary glands are a modified and highly specialized type of sweat gland [14]. Mammary buds begin to develop during the sixth week as solid downgrowths of the epidermis into the underlying mesenchyme [14]. Polythelia occurs in about 1% of the female population and is an inheritable condition [14]. An extra nipple usually develops just inferior to the normal breast [14]. Supernumerary mammary tissue very rarely occurs in a location other than along the course of the mammary ridge [14].

Gastrulation is the process that converts the embryo from two layers to three, by interposition of a mesoblastic layer between the epiblast and the hypoblast [15, 16]. At the end of stage 6, usually at 15 days of development, the process of gastrulation begins [15]. A linear thickening, called the primitive streak, appears in the epiblast, in the midline of the caudal aspect of the embryonic disk [15, 16]. The primitive streak is the site and source of the majority of migrating cells that form the middle and inner layers of the embryo [15, 16]. At the caudal end of the primitive streak is an area of fusion of the two cell layers, similar to the rostral prochordal plate [15, 16]. This site is the circular cloacal membrane, which is the future location of the anus and urogenital structures [15, 16]. Cellular proliferation increases the length of the primitive streak, and a thickening forms at its rostral end, called variously the primitive node or Hensen's node [15, 16]. Cells from the epiblast move into the primitive streak and groove, separate from the epiblast, and migrate rostrally between the epiblast and hypoblast to form the mesoblast (gastrulation), thus creating the earliest stage of the trilaminar embryo [15, 16]. Cells passing from Hensen's node cranially in the midline between the epiblast and hypoblast form the notochordal process, whereas prospective mesodermal cells of the primitive streak will form the remaining mesoderm [15–17]. Prospective notochordal cells within Hensen's node are the first mesodermal cells to ingress and pass cranially in the midline [17]. These cells will form medial mesodermal structures or prospective somitic mesoderm [17]. Somitic mesoderm subsequently becomes segmented to form discrete blocks of tissue, the somites [17]. The somites are bilaterally paired structures that lie on either side of the midline notochord and contribute to the formation of the vertebrae and ribs, as well as the muscles of the trunk and the dermis of the body wall [17]. Dias and Walker [18], in their theory about complex dysraphic malformations, proposed that split cord malformations and other related complex dysraphic malformations arise during a time when prospective anlagen from all three germ layers are in intimate association, that is, while they are being laid down during gastrulation [18]. The events of this model are contrasted with those of normal development. According to the theory of Dias and Walker [18] to explain the embryogenesis of split cord malformations and related malformations through a failure of midline axial integration during gastrulation, the primitive streak is abnormally wide and the prospective notochordal cells in Hensen's node begin ingressing more laterally than normal [18]. These notochordal precursors remain separate and develop independently over a variable portion of their length, and similarly, bilaterally paired prospective neuroepithelial cells remain separate and differentiate independently to produce two hemicords [18]. Laterally displaced somitic tissue would form an abnormally widened spinal canal with numerous associated vertebral segmentation anomalies, including sagittally clefted (butterfly) vertebrae, hemivertebrae, missing vertabrae (as is seen in our cases and other segmental costovertebral malformations mentioned in our paper) [18]. The intervening space between the paired

hemicords is composed of pluripotent primitive streak cells and could give rise to a variety of tissue types from any of the three primary germ layers [18]. Finally, secondary problems with subsequent primary neurulation of each or both of the hemicords could produce associated NTDs through a failure of segmental neurulation (producing myelomeningoceles if both hemicords are involved or hemimyelomeningoceles if only one hemicord is involved); secondary neurulation defects include skin-covered variants of spina bifida, such as meningocele, lipomas, lipomyelomeningoceles or dermal sinus tracts due to an abnormality of cutaneous ectodermal separation [18].

The discovery of particular 'homeobox' genes that direct segmental development provides evidence of direct genomic control of bony or cartilaginous segmentation [17, 19]. The formation of the neural tube both precedes and continues during somitic segmentation [17]. The neural tube provides the principal stimulus for somitic segmentation [17]. Prospective somitic cells within the paraxial mesoderm are located immediately subjacent to the neural plate during early neurulation, extending as far laterally as the lateral edges of the neural plate [17]. As neurulation proceeds, these cells occupy a position immediately lateral to the developing neural tube [17].

Recently, there has been a report on 16 children: 12 had SCD, and 4 with STD had some rare form of NTD; 4 patients had segmental spinal dysgenesis, 6 showed caudal regression syndrome with spinal cord involvement ('blunt conus' or low-lying spinal cord with lipoma), 2 cases presented with diastematomyelia, 2 had hydromyelia, 1 had thoracic anterior meningocele and 1 had sacral posterior arch schisis [20]. All of the cases with SCD and STD showed some rare form of NTD. Cama et al. [20] proposed that the association of SCD with NTDs may be a common developmental anomaly, or that different genes interact to give this complex phenotype. They concluded that the less rare association of segmental costovertebral anomalies and NTDs could be related to an early gastrulation defect that sometimes progresses and then involves primary and secondary neurulation.

We report on 3 children with SCD. Two of them showed some form of NTD: 1 patient had lipomyelomeningocele (malformation due to secondary neurulation), and 1 patient had open myelomeningocele (malformation due to primary neurulation).

The common association of segmental costovertebral malformations with NTDs could be related to an early gastrulation genomic defect, or one after gastrulation when there are two independent somitic columns. The latter sometimes progresses and then involves primary and secondary neurulation. Also, the association of SCD with NTDs could be related to the interaction of different genes, resulting in this complex phenotype. Therefore, additional genetical and embryological studies are necessary to provide evidence of an etiological link between SCD and NTD.

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