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SMD Kozlowski type caused by p.Arg594His substitution in TRPV4 reveals abnormal ossification and notochordal remnants in discs and vertebrae

Tadeusz Bieganski¹, Peter Beighton², Maciej Lukaszewski¹, Krzysztof Bik³, Lukasz Kuszel⁴, Ewa Wasilewska⁵, Kazimierz Kozlowski⁶, and Malwina Czarny-Ratajczak^{4,7,*}

¹Department of Diagnostic Imaging, Polish Mother's Memorial Hospital - Research Institute, Lodz, Poland ²Division of Human Genetics, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa ³Department of Orthopaedics, Polish Mother's Memorial Hospital - Research Institute, Lodz, Poland ⁴Department of Medical Genetics, Poznan University of Medical Sciences, Poznan, Poland ⁵Department of Radiology, Children's Hospital, New Orleans, USA ⁶Department of Medical Imaging, The Children's Hospital at Westmead, Sydney, Australia ⁷Department of Medicine, Tulane University, School of Medicine, New Orleans, Louisiana

Abstract

Spondylometaphyseal dysplasia Kozlowski type (SMDK) is a monogenic disorder within the *TRPV4* dysplasia spectrum and has characteristic spinal and metaphyseal involvement. We report skeletal MR imaging in a two-year-old patient who manifested typical clinical and radiographic features of SMDK. The diagnosis was confirmed by molecular analysis which revealed a mutation NM_021625.4:c.1781G>A - p.(Arg594His) in exon 11 of the *TRPV4* gene. We have documented abnormalities in endochondral formation of the long and short tubular bones as well as round bones of the wrists and feet. The vertebral bodies had increased thickness of hyaline cartilage which enveloped ossification centers. The vertebrae and discs also had abnormalities in size, shape and structure. These anomalies were most likely the consequence of notochordal remnants presence within the intervertebral discs and in the vertebral bodies. The advantages of MR imaging in bone dysplasias caused by *TRPV4* mutations are emphasized in this article.

INTRODUCTION

Spondylometaphyseal dysplasia Kozlowski type (SMDK; MIM: 184252) is a relatively common autosomal dominant entity within a heterogeneous group of about 30 different disorders with abnormalities of the vertebrae and metaphyses of the tubular bones

Corresponding author: Malwina Czarny-Ratajczak, Ph.D., Tulane School of Medicine, Department of Medicine, 1430 Tulane Ave., SL-12, New Orleans, LA 70112, phone: (504)-988-3090, mczarnyr@tulane.edu.

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CONFLICT OF INTERESTS

The authors declare that they have no competing financial interests.

[Lachman, 2007]. It is one of the most well-defined clinically spondylometaphyseal dysplasias for which the molecular basis has been elucidated. *TRPV4* mutations identified in patients with this disorder affect calcium permeable ion channels [Krakow et al., 2009; Warman et al., 2011].

The *TRPV4* gene (MIM: 605427) has been mapped to chromosome 12 (*12q24.11*) and is composed of 15 exons [Wissenbach et al., 2000; Liedtke et al., 2000]. Mutations in *TRPV4* have also been identified in other skeletal disorders: digital arthropathy-brachydactyly (MIM: 606835); [Lamande et al. 2011], brachyolmia type 3 (MIM: 113500); [Rock et al., 2008], Maroteaux type of spondyloepiphyseal dysplasia (MIM: 184095); [Nishimura et al., 2010], parastremmatic dwarfism (MIM: 168400); [Nishimura et al., 2010], and in lethal and nonlethal autosomal dominant metatropic dysplasias (MIM:156530); [Krakow et al., 2009; Camacho et al., 2010]. These six skeletal disorders form an overlapping phenotypic spectrum of increasing severity, from mild digital arthropathy-brachydactyly to more severe forms, with metatropic dysplasia at the end of the scale [Andreucci et al, 2011; Nemec et al, 2012; Nilius and Voets, 2013].

TRPV4 mutations also cause congenital spinal muscular atrophy (MIM: 600175), scapuloperoneal spinal muscular atrophy (MIM: 181405) and hereditary motor and sensory neuropathy type IIC (MIM: 606071). In 2012, Cho et al. reported three individuals who had an overlapping skeletal dysplasia/peripheral neuropathy phenotype caused by heterozygous *TRPV4* missense mutations.

The majority of mutations detected to date have been gain-of-function mutations which result in activation of the TRPV4 channel; however, the mechanism through which this activation results in skeletal dysplasia and/or peripheral neuropathy remains unclear.

We report a two-year-old boy with SMDK and mutation identified in *TRPV4*, including proximal tibial corner pseudo-fractures and delayed carpal and tarsal ossification. These features, together with MRI of thick cartilage of vertebral bodies, reflect abnormalities in chondrocyte differentiation in the growth plate of the long bones and endochondral ossification of the flattened vertebral bodies. We consider embryological remnants of the notochord in abnormal intervertebral discs and persistent notochordal canals within the vertebral bodies as significant findings, as they indicate that pathophysiological studies in SMDK and other dysplasias of *TRPV4* family could be of considerable interest.

MATERIALS AND METHODS

Clinical analysis

We examined a 17-month-old proband who was referred to the orthopedist due to his varus deformity of knees, gait disturbances and short stature. Radiographs of the extremities, spine, pelvis and skull revealed abnormalities which were consistent with SMDK. This study was approved by the local Bioethical Research Committee.

MRI Analysis

MRI studies of the spine and hands were performed utilizing 3T system (Achiva 3.0 T Tx, Philips Healthcare). The spine protocol included T1 and T2 turbo spin-echo sequences (T1W TSE SENSE - slice thickness 2.5 mm, matrix size 325, flip angle 85 deg; TE 8 msec, TR 519 msec and T2W TSE SENSE- slice thickness 3mm, matrix size 232, flip angle 90 deg, TE 95 msec, TR 4435 msec) and T2 weighted images with fat saturation (T2W SPAIR SENSE -matrix size 315, flip angle 90 deg, TE 72 msec, TR 3536 msec). The latter images were used as a baseline to differentiate specific components of the vertebral column based on their signal characteristics. The cartilaginous structures of the carpal region were studied with a cartilage dedicated sequence (T1W image with WatSc - water selective cartilage scan - sequence - TR 20 msec, TE 5,3 msec; voxel $0.23 \times 0.23 \times 0.25$; FOV 12×120 mm). The cartilage thickness of vertebral bodies, ossification centers and discs was evaluated in sagittal plane of the cervical, thoracic and lumbar spine and analyzed quantitatively with the method described by She et al. [1991]. The cartilage was defined as “the hyaline cartilage, which enveloped the ossification center and formed the endochondral growth layer”. The thickness of cartilage was measured at the inferior aspects of the vertebral bodies in two locations: the center and the anterior 1/4 segment of the vertebral body (Fig.1). Subsequently, that data was used to calculate ratios of these parameters (Tab 1). The height (thickness) of discs and vertebral bodies was also measured. The vertebral body was defined as “the ossification center together with superior and inferior hyaline cartilage layers.” The disc was defined as “the intervertebral structure between the hyaline cartilage layers of two adjacent vertebrae.” The ratio of the disc to vertebral body height was calculated and compared with data from normal infants [Sze et al., 1991].

Genetic Analysis

Molecular analysis of the *TRPV4* gene (NM_021625.4 GenBank reference sequence) in reported patient was focused on the coding regions, where mutations frequently occur. We designed primers for PCR amplification of exons 5–6 and 9–13, which was based on genomic DNA isolated from lymphocytes and followed by Sanger sequencing of PCR products using routine protocol.

RESULTS

Clinical and Radiological Findings

The affected proband was born at term to young healthy parents. His birth weight was 3,050 g and apgar scores were 7 and 9 after 1 and 2 minutes. No abnormalities were observed at birth; however, after 12 months his parents noted shortening of his trunk with marked kyphosis in the thoracic spine and hyperlordosis of the lumbar spine. He also had difficulty walking, and these abnormalities progressed with age. The proband was examined in an orthopedic outpatient clinic at the age of 17 months. At this time his height was 76 cm (< 3rd centile) and his weight was 12,160 g (50th centile). His neck and trunk were short with marked thoracic kyphosis and lumbar hyperlordosis. In addition, shortening of lower extremities, varus deformity of the knees and waddling gait were observed. His photograph taken at the age of 26 months (Fig. 2) shows some of these features. Ultrasound examination of the knees demonstrated genu varum with small bony fragments at the medial aspects of

the proximal tibial metaphyses. Skeletal survey revealed changes characteristic of SMDK (Fig. 3–5), including platyspondyly. The pelvis had flared iliac wings, short sacroiliac notches, horizontal acetabula and short femoral necks. Epiphyses of the tubular bones were relatively normal; however, metaphyses were widened with an irregular trabecular pattern. In the hands, there was shortening of the tubular bones, and the carpal and epiphyseal ossification centers were absent. The skull was normal.

At ages 19 and 22 months small bony fragments were demonstrated at the proximal, medial tibial metaphyses and resembled corner fractures (therefore called corner pseudo-fractures). They were absent at the follow-up examination at age 25 months (Fig. 3A–B). Due to progressive varus deformity of the knees, bilateral tibial osteotomies were performed at the age of 25 and 29 months.

Radiographs of the patient's feet, obtained at the age of three, demonstrated short metatarsals with wide and irregular margins and cupped configuration of the distal metaphyses. There was delayed appearance of the ossification centers of the first and third cuneiform. The phalangeal epiphyses were absent at the age of 3. The middle and distal phalanges were short. The talus and calcaneus were noted to have regular, smooth contour (Fig. 3D).

In the upper extremity, humeral metaphyses were broad with undermodeling of the proximal shafts (Fig. 4A). The carpal bones and epiphyseal ossification centers of the short tubular bones of the hand were markedly delayed and ossification centers were absent on hand radiographs. The metacarpals and phalanges were irregular (Fig. 4B). MR images of the left hand, obtained eight months later, showed presence of well formed cartilaginous carpal "bones" and metacarpal epiphyses, however, without signs of ossification. The II, III, IV and V metacarpals also demonstrated well-formed cartilaginous and unossified proximal epiphyses (Fig. 4C). Spinal radiographs showed pronounced thoracic kyphosis, lumbar hyperlordosis and platyspondyly. Wide intervertebral discs spaces and anterior wedging of lumbar and thoracic vertebral bodies were observed. The cervical vertebrae were more uniformly flattened and anteriorly rounded. Coronal clefts were noted in some of the vertebral bodies. The odontoid process was not visible (Fig. 5A).

MRI of the lumbar and thoracic spine, obtained midline in sagittal and coronal planes, revealed concave configuration of the vertebral bodies and convexity of the adjacent intervertebral discs (Fig. 5B – D). The odontoid process was present but completely composed of cartilage (Fig. 5D). Enlarged vertebral pedicles were apparent in the coronal plane (Fig. 5E). The high contrast resolution of MRI facilitated precise visualization and measurement of specific components of the vertebral column (Fig. 1). The dimensions of the entire vertebral bodies as well as their specific components including ossification centers, adjacent cartilages and also discs are shown in Table I and Table II. Of note, there was gradual increase in size of all spinal elements i.e. ossification centers, vertebral cartilages and discs in caudal direction with the largest dimensions recorded in the lumbar segment. The differences in the thickness ratios of vertebral cartilage to ossification centers, observed in the thoracic and lumbar regions, depended mainly on variations in height within the ossification centers where the measurements were obtained: the mean ratio when measured

in the center of the ossification center was in range of 0.80 – 0.98 and ratios of 0.35–0.90 were obtained when measurement was performed in anterior 1/4 portion of the vertebral body (Table I). The vertebral discs had lenticular shape throughout the spine and were relatively high when compared with the vertebral bodies. The disc to vertebral body height ratios were in range of 0.58 – 1.19 (Table II).

The intervertebral disc space, as seen on radiographs, consists of a disc and two layers of hyaline cartilage from two adjacent vertebral bodies.

Close analysis of the intervertebral discs on high contrast resolution T2 weighted imaging, revealed a vertical, rod-like structure, which demonstrated high T2 and low T1 signal intensity and thought to represent notochord remnant. The vertical orientation and central location was best appreciated in sagittal plane in the thoracic and lumbar segments (Fig. 5B) and in coronal plane in the cervical and lumbar spine (Fig. 5C). In axial plane, the notochord remnants had oval shape throughout the spine (Fig. 6A), which was confirmed by measuring AP and R-L dimensions at four cervical, nine thoracic and five lumbar discs (Table III). The R-L dimensions were larger (range 3.9 – 5.9 mm) when compared to AP measurements (range 2.0 – 2.9 mm). In axial plane, the notochord remnants had ellipsoidal shape throughout the spine, which was confirmed by measuring AP and R-L dimensions at four cervical, nine thoracic and five lumbar discs (Fig. 6A, Table III). The R-L dimensions were larger (range 3.9 – 5.9 mm) when compared to AP measurements (range 2.0 – 2.9 mm). In direct extensions of the aforementioned notochord remnants, there were vertically oriented channels running through the central aspect of the vertebral bodies. They demonstrated signal characteristics that of cartilage and thought to represent persistent notochord canals. Similarly to notochord remnants within discs, these canals largest dimensions were oriented in R-L direction, giving them ovoid configuration in axial plane (Fig. 6B, Table III). In the thoracic and lumbar regions, cylindrical forms were demonstrated (Fig. 6B, Table III).

Genetic Findings

Analysis of exons 5–6 and 9–13 revealed that the patient was heterozygous for a c.1781G>A mutation in exon 11 of *TRPV4* [NM_021625.4:c.1781G>A - p.(Arg594His)], using GenBank reference sequence.

This mutation is recurrent in patients with SMD Kozłowski type, and position c.1781 in exon 11 is a frequently mutated hotspot in this disorder. At the cellular level, this gain-of-function mutation results in activation of the calcium channel. This channel contains three ankyrin repeats located at the amino terminus and six putative transmembrane domains with a cation-permeable pore region located between transmembrane domains 5 and 6 [Phelps et al., 2008].

DISCUSSION

The patient we studied had the characteristic clinical and radiographic features of SMDK [Kozłowski et al., 1967; Spranger et al., 2002; Nural et al., 2006; Lachman, 2007; Nemec et al., 2012]. The only findings not previously reported were the symmetrical triangular bony fragments at the proximal, medial aspects of the tibiae (Fig. 3A). Their transient nature is

interesting; they were documented by both ultrasound and plain radiographs at the age of 17 – 22 months but were absent at 25 months (Fig. 3B). These triangular bony fragments are most likely associated with genu varum deformity. Their transient appearance may be the result of abnormal ossification of the growth plates. This process may have the same etiology as the radiolucent bands in metaphyseal regions in SMDK [Nishimura et al., 2012]. Similar trapped cartilage islands were noted in metatropic dysplasia [Camacho et al., 2010] as well as in other bone dysplasias caused by constitutive activated *TRPV4* mutations [Kang et al, 2012].

The phenotype of our patient also shares other radiological features with metatropic dysplasia, which include: delayed carpal ossification (Fig. 4B), cranio-caudal shortening of iliac wings, which is also observed in brachyolmia, flat acetabular roofs (Fig. 3C), platyspondyly and metaphyseal expansion of the long tubular bones with irregular ossification of the physal surface (Fig. 3A, 3B). Moreover, the following overlapping features with brachyolmia were noted: metaphyseal lesions of short tubular bones of hands (Fig. 4B), platyspondyly (Fig. 5A – E) and broad and short ilia (Fig. 3C). Radiographic similarities between these three entities of *TRPV4* spectrum were discussed in details by Nemec et al. (2012) and by Nishimura et al. (2012).

On MR T2 weighted images the vertebral cartilage is hypointense in comparison to signal intensities of the adjacent disc and vertebral ossification center. The thickness ratio of cartilage to the ossification center could indicate activity of ossification process in the vertebral bodies. In our patient the cartilage appears to be the most narrow in the lumbar spine, with a cartilage to ossification center ratio (C/O) of 0.34 when measured at the thickest part of the ossification center (Fig. 1, Table I). This value is in the range of normal for lumbar vertebral bodies in neonates (0.25 – 0.50), while for age group 18–24 months, corresponding with our patient, varies from minimal to 0.125 [She et al., 1991]. The vertebral bodies of the cervical and thoracic spine contain cartilage layers which are much thicker than those of the lumbar region, with mean C/O values of 0.91 and 0.50, respectively (Table I). These data indicate that cartilaginous components of vertebral bodies are markedly thicker in this reported patient with SMDK at the age of 2 years and 4 months, reflecting abnormal mineralization of axial skeleton.

This finding seems to be comparable to the abundant and thick cartilage at the ends of the long bones observed in two patients with lethal metatropic dysplasia [Camacho et al., 2010]. Histological studies of the growth plates in these neonates revealed abnormal chondrogenesis and disrupted endochondral ossification [Camacho et al., 2010].

The thickness of discs and vertebral bodies increases in parallel along the spine, from the cervical to the lumbar region, and the mean ratios of disc/vertebra for particular spinal regions do not show significant differences. The calculated value for the lumbar spine ratio is 0.85 (Table II) and is much higher if compared with the corresponding values for normal neonates or two-year-old children (0.4 or 0.25, respectively), [Ho et al., 1988; She et al., 1991]. This ratio indicates the extent of the abnormal relationship between the high discs and flattened vertebral bodies in SMDK.

The presence of notochordal remnants on MR scans was an unexpected finding. The notochord is an embryonic midline structure, which develops during the third week of gestation and exists transiently. It plays an important structural role, serving as the primitive axial skeleton of the embryo during vertebral column formation [Fleming et al., 2001; Stemple, 2005]. The notochord also produces several factors, which signal to surrounding tissues. These signals induce formation of the perinotochordal tube with a metameric pattern. This tube develops into nuclei pulposi of the intervertebral discs, and into vertebrae [Smits and Lefebvre, 2003]. The notochord runs through the middle of each vertebra and each disc space, which simultaneously undergoes a series of changes. The notochordal cells are removed from vertebral bodies and relocated into intervertebral regions, where they proliferate, forming the nuclei pulposi. At the cartilaginous stage, notochordal cells usually disappear and notochord ossification occurs. Only a small number of notochordal cells can be detected in the nucleus pulposus at full term [Peacock, 1951; Kyriakos, 2011]. If notochordal cells are present during development of vertebral bodies, cells surrounding the notochord do not differentiate properly and ossification of embryonic cartilage is affected. This process results in persistence in the intravertebral notochordal space of a cartilaginous column known as the notochordal canal [Taylor, 1972]. Studies of human embryos and fetuses have demonstrated that notochord remnants persist along the notochordal evolutionary pathway [Peacock, 1951; Taylor, 1972].

The intervertebral discs throughout the whole embryonic period are biconcave in the sagittal median plane, while their central parts, the so-called notochordal areas within the discs, are biconvex and contain a homogenous, semifluid substance with a limited number of notochordal cells (Peacock, 1951). Similar components of the fetal notochordal cavity have been observed in histologic specimens taken from notochordal remnants. They present most often as ectopic lesions, and usually with a hyperintensive signal on MRI T2 weighted images [Christopherson et al., 1999; Kyriakos et al., 2003; Mehnert et al., 2004; Wang et al., 2008; Oner et al., 2009].

The notochordal remnants in the patient we studied had some specific features and differed quantitatively and qualitatively from the normal neonatal appearance of notochordal rests, and also from ectopic benign notochordal tissue, localized in a single vertebra or disc. The abnormalities in this patient are a generalized phenomenon, with segmental lesions in the whole vertebral column. The discs and vertebral bodies both manifest an abnormal size, shape and structure; the latter are also expressed in an altered signal intensity of MR images. The discs are high and convex in the lumbar and thoracic regions. Instead of being fusiform, the horizontal plate of the nucleus pulposus is in the equator of the discs in normal neonates [Peacock, 1951; Ho et al., 1988], while the vertical highly hydrated rod structure occupies the middle space. This appearance closely resembles the notochord image of a human embryo at the very early stage of notochordal evolution, before its intervertebral expansion [Peacock, 1951]. The lumbar and thoracic vertebral bodies in the boy with SMDK are fish-shaped with funnel depressions of the upper and lower surfaces.

Extensions of the rod-like structures within the vertebral bodies contain cartilaginous columns which represent the notochordal canal. These very rare lesions were found in 3 of 57 investigated children, only in infants below the age of 10 months and only in single

lumbar and thoracic vertebrae [Taylor, 1972]. The persistent notochordal canal in most of the vertebrae (Table III) and the abnormalities in almost all discs in the SMDK patient present qualitative differences from those described in apparently normal vertebral columns in infants.

Plain radiography is the conventional modality for diagnosis of bone dysplasias. Radiological survey will likely remain the gold standard for clinical diagnosis of these disorders, including SMDK, due to its simplicity, wide accessibility and well-defined features of bone dysplasias. However, MR scanning, as shown in this reported patient, is providing important new data for comprehensive evaluation of the skeletal system, especially in young children with marked cartilaginous components. MRI provides superior images and permits easier interpretation of anatomical details. Additionally, by documenting anatomical abnormalities MRI is better at predicting the course of the condition, and superior to plain radiographs in the design of appropriate treatment. Our data show two examples of more effective documentation of anatomical abnormalities by MRI than by plain radiography. At the age of 3 years, cervical spine radiography revealed odontoid hypoplasia (Fig. 5A). Eight months earlier MR imaging showed a normal cartilaginous odontoid process (Fig. 5D). On this basis, it can be concluded that plain radiography is not appropriate for diagnosis of odontoid hypoplasia in disorders with abnormal or retarded mineralization, such as SMDK and allied bone dysplasias.

The persistence of notochordal canals in vertebrae has been reported as being associated with vertebral clefts, in coronal and/or in sagittal planes [Rathke, 1959; Taylor, 1972]. Our patient also has the appearance of coronal clefts on radiographs of the cervical spine (Fig. 5A). MRI study facilitated interpretation of this radiographic finding as an artifact of X-ray imaging. These radiographic pseudoclefts result from the diminished attenuation of the X-ray beam by cartilage columns, or other not ossified soft tissue material in the middle of vertebral bodies. Axial MR imaging of vertebral bodies in the affected boy did not show any clefts.

Although this article presents new imaging data showing abnormalities in vertebral bodies and intervertebral discs of the patients with SMDK, this should be followed by MR spinal studies in other patients with SMDK at different ages and in patients with metatropic dysplasia or brachyolmia, which belong to the *TRPV4* spectrum of disorders. These follow-up studies will provide further insight as to whether our findings are representative for SMDK and other spondylometaphyseal dysplasias.

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Figure 1.

Sagittal T2-weighted magnetic resonance image of the spine in midline demonstrating measurements of spinal structures used for ratios calculation: ossification center (OC), vertebral cartilage (C), disc (D), vertebral body (V) measurements obtained in the center of the vertebral bodies and intervertebral discs.

*Measurements obtained at anterior 1/4 segment of vertebral bodies

Figure 2.
Photograph of the patient at 26 months of age. Note shortening of the trunk, varus deformity of the left knee and the right tibia after surgical correction.

Figure 3.

A: AP radiograph of bilateral lower extremities obtained at 22 months of age demonstrates bilateral genu varum with metaphyseal widening and fragmentation of the medial aspect of the proximal tibial metaphyses (corner pseudofractures). B: AP radiograph of bilateral knee taken at 25 months of age, demonstrates healing of the proximal medial tibial pseudofractures with improvement of the genu varum. C: **AP pelvis radiograph obtained at age of 21 months shows: flared iliac wings, short sacroiliac notches, horizontal acetabula and short femoral necks with widening of the proximal femoral metaphyses**

and mild coxa vara. D: AP radiograph of the right foot at the age of three years demonstrates an apparent shortening of metatarsals with scalloping of metaphyses most pronounced distally. Broad first metatarsal and proximal phalanges; hypoplastic or absent middle and distal phalanges II – V.

Figure 4.

A: AP radiograph of the left upper extremity at the age 22 months shows broad metaphyses with undermodeling of the proximal shaft. B: AP radiograph of the left hand at the age 20 months with mild metaphyseal scalloping and delayed appearance of the carpal and epiphyseal ossification centers. C: MRI of the left hand at age 28 months. T1W image of WatSc sequence (TE 5.3 msec, TR 20 msec). Normal shape of the unossified carpal “bones” is observed.

Figure 5.

A: Lateral view of the cervical spine of three-year-old patient. Note platyspondyly with anteriorly rounded flat vertebral bodies and coronal clefts (thin arrows). Odontoid process is not visible giving the appearance of the odontoid hypoplasia (thick arrow). B–E: MRI of the entire spine in sagittal plane using T2W SPAIR SENSE (TE 72 msec, TR 3536 msec) obtained at 28 months of age. B–D: Vertebral bodies are formed by ossification centers surrounded by vertebral hyaline cartilage. Thoracic and lumbar discs are concave with high signal intensity. Well-depicted high signal intensity structures are evident within the center

of intervertebral discs representing notochord remnants (thin arrows). There are low signal intensity columns in the middle of the vertebrae thought to represent persistent notochord canals (thick arrows). C: The curve-planar reformation was used for correction of the kyphoscoliosis and delineation of the entire vertebral column on a single coronal image. D: Sagittal view of the cervical spine with intravertebral, low signal intensity cartilaginous structures (thin arrows) corresponding to apparent vertebral body clefts demonstrated on the lateral radiographs (5A). The odontoid process is present but completely composed of cartilage therefore not visible on corresponding radiographs (thick arrow). E: Thoracic vertebral bodies with enlarged pedicles (arrows).

Figure 6. MR T2 weighted image of the lumbar spine in axial plane. A: An oval, high signal intensity structure in the center of the lumbar intervertebral disc thought to represent a notochordal remnant (arrows). B: There is a hypointense structure within the lumbar vertebral body representing the notochordal canal (arrows).

Table I

Thickness (mm) of Cartilage and Ossification Centers of Vertebral Bodies.*

	Cartilage** in the center of vertebral body	Ossification in the center of vertebral body	C/O*** ratio in the center of vertebral body	Cartilage*** anterior 1/4	Ossification Center anterior 1/4	C/O*** ratio anterior 1/4
C3 – C7	2.0 ± 0.5	2.1 ± 0.3	0.98 ± 0.35	2.0 ± 0.1	2.2 ± 0.2	0.91 ± 0.06
Th–Th12	2.2 ± 0.4	2.6 ± 0.7	0.87 ± 0.15	2.2 ± 0.3	4.6 ± 1.2	0.50 ± 0.11
L1–L5	3.6 ± 0.4	4.5 ± 0.5	0.80 ± 0.13	3.1 ± 0.2	9.0 ± 1.0	0.34 ± 0.03

* Measurements obtained in sagittal plane in the center and the anterior 1/4 portion of the vertebral body and ratio of these parameters (x ± SD)

** Cartilage along the inferior aspect of the vertebral body

*** C - cartilage; O - ossification center

TABLE II

Thickness of Discs* and Vertebral Bodies* (mm)

	Discs		Vertebrae		Disc/Vertebra	
	Range	x ± SD	Range	x ± SD	Range	x ± SD
C3–C7	3.1–5.1	4.0 ± 0.6	5.0–5.5	5.3 ± 0.2	0.58–1.02	0.76 ± 0.14
Th1–Th12	4.8–7.2	5.8 ± 0.8	4.7–8.9	6.6 ± 1.2	0.70–1.19	0.90 ± 0.15
L1–L5	7.7–10.6	9.3 ± 1.0	10.5–11.7	11.0 ± 0.4	0.73–0.96	0.85 ± 0.09

* Measured in the center of the vertebral body

TABLE III

Size of Notochord Remnants (mm; x ± SD) in Discs and in Vertebral Bodies

Region	Remnants in Discs				Remnants in Vertebral Bodies (notochordal canal)			
	n	AP*	L**	AP/L	n	AP	L	AP/L
Cervical	4	2.0 ± 0.0	3.9 ± 0.2	0.5 ± 0.0	3	2.3 ± 0.5	3.7 ± 0.2	0.6 ± 0.2
Thoracic	9	2.1 ± 0.2	2.7 ± 0.6	0.8 ± 0.2	9	2.9 ± 0.5	3.4 ± 0.9	1.0 ± 0.2
Lumbar	5	2.9 ± 0.7	5.9 ± 1.9	0.5 ± 0.1	5	2.3 ± 0.4	2.7 ± 0.8	0.9 ± 0.2

* AP anterior-posterior direction

** L lateral direction