Dysspondyloenchondromatosis: Another COL2A1-Related Skeletal Dysplasia?

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Key Words

COL2A1 · Enchondromatosis · Skeletal dysplasia · Type II collagenopathy

Abstract

Dysspondyloenchondromatosis (DSC) is a rare skeletal dysplasia that has currently been classified into the group of spondylometaphyseal dysplasias. To date, only 12 affected individuals have been reported. All cases are sporadic, and the etiology remains unknown. Distinctive features of DSC are anisodysplasia and enchondroma-like lesions in the metaphyseal and diaphyseal portions of the long tubular bones. Affected individuals usually develop kyphoscoliosis and asymmetric limb shortening at an early age. Interestingly, some of the skeletal changes overlap with spondyloepimetaphyseal dysplasia (SEMD) Strudwick type, a rare type II collagen disorder. Based on this resemblance we postulated that DSC may be allelic to SEMD Strudwick type and therefore performed a COL2A1 analysis in an affected boy who was diagnosed as having DSC at the age of 3 years. The identification of a novel heterozygous COL2A1 missense mutation (p.Gly753Asp) in the proband confirms our hypothesis and suggests that DSC may be another type II collagen disorder.

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Dysspondyloenchondromatosis (DSC) is a rare skeletal dysplasia, which was proposed as a distinctive entity by Freisinger et al. [1993]. So far, 12 affected individuals have been reported [Mainzer et al., 1971; Spranger et al., 1978; Azouz, 1987; Lerman-Sagie et al., 1987; Freisinger et al., 1993; Kozlowski et al., 1994; Haga et al., 1998], and the radiologic images of 3 cases were illustrated in standard textbooks of bone dysplasias [Spranger et al., 2002; Lachman, 2007]. All cases are sporadic, and the etiology has not been elucidated up to date. The hallmark features of DSC are irregularly shaped vertebral bodies (anisodysplasia) and enchondroma-like lesions in the metaphyseal and diaphyseal parts of the long tubular bones. The former may cause progressive kyphoscoliosis, and the latter may result in asymmetric limb shortening [Freisinger et al., 1993; Kozlowski et al., 1994]. DSC was once considered to be a form of generalized enchondromatosis, but the disorder has currently been classified into the group of spondylometaphyseal dysplasias [Warman et al., 2011].

Heterozygous mutations in the type II collagen gene (COL2A1) induce a wide spectrum of skeletal dysplasias collectively termed type II collagenopathies [Spranger et al., 1994; Nishimura et al., 2005]. The most constant radiographic features of type II collagenopathies are spon-

Fig. 1. Radiographs at the age of 3 years. Note the severe thoracic scoliosis with misshapen vertebral bodies and enchondroma-like metaphyseal changes with metaphyseal expansion and unequal length of the legs. The right proximal femoral epiphysis is ossified, while the left is not.

Fig. 2. Radiographs at the age of 10 years. The radiological manifestations are essentially the same as those at the early age. However, noted are progressive scoliosis, less conspicuous metaphyseal expansion of the femora and metaphyseal radiolucencies deeply extending into the diaphysis of the right femur. The proximal femoral epiphyses are well ossified together with coxa vara. The proximal humeral metaphyses are expanded with enchondroma-like lesions. The ulnae and radii are bowed and their distal metaphyses are irregular.

dylar and epiphyseal involvement of the skeleton. However, a subset of type II collagenopathies shows predominant metaphyseal involvement with only mild epiphyseal changes [Walter et al., 2007], such as in spondyloepimetaphyseal dysplasia Strudwick type (SEMD-S) [Anderson et al., 1982; Tiller et al., 1995]. In some cases with SEMD-S, the metaphyseal anomalies impair physeal growth and lead to limb asymmetry [Walter et al., 2007]. Craniofacial involvement with cleft palate, vitreoretinal degeneration,

severe myopia, and hearing impairment are characteristic clinical features of type II collagenopathies. Cleft palate and minor facial dysmorphism have been reported in DSC as well [Kozlowski et al., 1994].

Given the phenotypic overlap between DSC and the type II collagen disorders (especially SEMD-S), both at the radiographic and clinical level, we were interested to investigate the possibility of *COL2A1* mutation in a boy with DSC.

Fig. 3. Spinal CT at the age of 13 years showing asymmetric ossifications of the vertebral bodies.

Case Report

The boy is the third child of a Japanese father and a Thai mother. The parents and his 2 siblings did not have a bone disease. He was delivered uneventfully at 37 weeks of gestation. Fetal ultrasonography apparently showed delayed bone maturation. Birth length was 41.0 cm (−3.1 SD) and birth weight 2,648 g (−0.5 SD). Cleft palate was noted at birth. He failed to thrive and underwent medical care in a community hospital until he was 6 months old. Motor development was delayed: he achieved head control at the age of 8 months and sat alone at the age of 18 months. He started walking at the age of 2 years and 3 months. However, then he started to develop gait disturbances and was wheelchair-bound when he was 4 years old. Language and mental development was normal. His IQ was 108 at the age of 10 years. At the age of 14 years and 8 months, his height was 103.0 cm (−9.8 SD) and his weight was 21.0 kg (−3.4 SD).

At the age of 3 years, he was diagnosed as having DSC. He had a flat midface with low-set ears and an everted lower lip. The radiological findings included severe thoracic scoliosis with misshapen vertebral bodies and enchondroma-like metaphyseal changes with metaphyseal expansion and unequal length of the legs (fig. 1). The right proximal femoral epiphysis was ossified, while the left was not. The radiological manifestations at the age of 10 years were essentially the same as those at the early age of 3 years. However, scoliosis was progressive. Metaphyseal expansion of the femora was less conspicuous than previously seen, while metaphyseal radiolucencies extended deeply into the diaphysis of the right femur (fig. 2). The proximal femoral epiphyses were now well ossified, but coxa vara was seen bilaterally. The proximal humeral metaphyses were expanded with enchondro-

Spondyloepimetaphyseal dysplasia Strudwick type

Fig. 4. Schematic representation of *COL2A1* mutations previously reported in SEMD-S, and a novel *COL2A1* mutation (p.Gly753Asp) in our patient.

ma-like lesions. The ulnae and radii were bowed. The distal radial and distal ulnar metaphyses were irregular. Spinal CT at the age of 13 years revealed asymmetric ossifications of the vertebral bodies (fig. 3).

DNA was extracted from the boy's blood, his siblings and the parents after informed consent. A sequence analysis of *COL2A1* was performed as described by Walter et al. [2007]. This revealed heterozygosity for a novel *COL2A1* mutation, c.2258 G>A (p.Gly753Asp) in exon 34. The mutation was present in the boy, but not in the other family members.

Discussion

The manifestations of previously reported cases with DSC are summarized in table 1. Affected individuals usually present with short length at birth. Kyphoscoliosis and limb length discrepancy usually become apparent later on in life but can be present at birth. The metaphyseal changes are scooped-out ossification defects reminiscent of perinatally hypophosphatasia. They evolve into longitudinally oriented radiolucencies, deeply extending into the diaphyses and resembling enchondromata. The vertebral changes are also peculiar. The vertebral bodies are irregularly ossified (anisospondyly) which mimics segmentation defects of the spine. Kozłowski et al. [1994] meticulously discussed the spinal deformity in

Table 1. Summary of our patient and the previously reported patients with DSC

	Our patient	Mainzer et al. (1971)	Spranger et al. (1978)	Azouz (1987)	Lerman-Sagie et al. (1987)	Freisinger et al. (1993)			
		Case 1	Case 1				Patient 1	Patient 2	Patient 3
Age	13 years	20 years	4 years	3 years	2 years and 7 months	3 years and 6 months	13 months		2 years and 6 months
Age at diagnosis	3 years	18 months	4 years	3 years	2 years and 7 months	3 years and 6 months	13 months		2 years and 6 months
Gender	male	female	male	male	female	male	male		female
<i>Clinical findings</i>									
Birth weight (g)	2,648	NA	2,400	2,500	2,450	2,950	3,450		2,850
Birth height (cm)	41	NA	40	NA	NA	40.5	43		41
Facial abnormality	flat mid-face; low-set ears	ND	posteriorly angulated auricles; short mandible	ND	ND	mild (not specified)	mild (not specified)		ND
Cleft palate	+	ND	ND	ND	ND	ND	ND		ND
Impaired visual acuity	–	ND	bilateral myopia and estropia	ND	ND	ND	ND		ND
Hearing impairment	–	ND	ND	ND	ND	ND	ND		ND
Mental development	normal	above average at birth	normal	ND	delayed	ND	ND		normal
Asymmetric limbs (detected age)	3 years		4 years	3 years	2 years and 7 months	at birth	13 months		17 months
Additional findings			lax, wrinkled skin		mucopolysac- chariduria				
<i>Radiological findings</i>									
<i>Vertebral changes</i>									
Malsegmentation-like	+	+	+	+	–	+	+		+
Hypoplasia/dysplasia	+	+	+	+	+	+	+		+
Scoliosis	severe	severe	mild	severe	severe	severe	mild		mild
<i>Enchondroma-like changes</i>									
Metaphyseal expansion	+	+	+	+	+	+	+		+
Extension to the diaphysis	+	+	+	+	–	+	–		–
Epiphyseal dysplasia	+	–	+	+	+	+	+		+
NA = Not available; ND = not described.									

NA = Not available; ND = not described.

DSC and raised the possibility that the vertebral abnormalities rather reflect ossification defects than true malsegmentation. This was supported by the spinal CT findings in the boy we report here.

As is well known, missense mutations in *COL2A1* that substitute a bulky amino acid for a glycine residue in the triple-helical region of the type II collagen chain lead to a broad spectrum of type II collagenopathies including SEMD-S [Spranger et al., 1994; Nishimura et al., 2005]. Metaphyseal involvement in SEMD-S is generally mild but sometimes conspicuous, with disruption of growth plate development and resulting in limb length discrepancy [Walter et al., 2007]. It is likely that the *COL2A1*

mutation (p.Gly753Asp) in the present boy is responsible for his DSC phenotype. This mutation clearly interferes with metaphyseal and vertebral ossification to a greater degree than that seen in SEMD-S. Mutations previously reported in SEMD-S are shown in figure 4 [Tiller et al., 1995; Kaitila et al., 1996; Tysoe et al., 2003; Walter et al., 2007]. Patients with the Gly283Arg or V783del mutations have limb asymmetry, but vertebral involvement was mild in these cases.

In conclusion, our data suggest that DSC is yet another member of the large family of type II collagen disorders. Study of additional cases with DSC is warranted to confirm this observation. It remains to be deter-

Kozlowski et al. (1994)				Haga et al. (1998)	Total
Case 1	Case 2	Case 3	Case 4		
5 years	4 years and 6 months	15 months	7 years	7 years	
1st day	1st day	4th day	5th day	1 year	
male	male	female	male	female	
3,045	3,500	2,100	3,650	3,060	
46	47.7	39.5	46	49	
ND	hypertelorism	flat mid-face	flat mid-face	ND	
ND	ND	ND	ND	ND	
ND	ND	ND	ND	ND	
ND	normal	probably normal	normal	ND	
ND	normal	delay	normal	ND	
at birth	2 years and 6 months	at birth	5 weeks	1 year	13/13
		laryngotracheo-malacia		lymphangio-hemangioma; rectovestibular fistula	
-	-	-	-	+	8/13
+	+	+	+	+	13/13
minimal	mild	none	severe	severe	12/13
					13/13
+	+	+	+	+	13/13
-	-	-	+	+	7/13
+	ND	ND	+	ND	9/10

mined why glycine substitutions within the triple-helical domain of the type II collagen molecule can result in such a broad spectrum of diseases, ranging from lethal phenotypes (achondrogenesis type II, hypochon-

drogenesis) to surviving short-stature phenotypes (spondyloepiphyseal dysplasia congenital, SEMD-S, DSC) with variable spondylo-epi-metaphyseal involvement on radiographs.

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