A case with oto-spondylo-mega-epiphyseal-dysplasia (OSMED): the clinical recognition and differential diagnosis

Kadri Karaer[1], Rasim Özgür Rosti[1], Deniz Torun[1], Hatice Tuba Sanal[2], Muhterem Bahçe[1], Şefik Güran[3]

Departments of [1]Medical Genetics, [2]Radiology and [3]Medical Biology, Gülhane Military Medical Academy, Ankara, Turkey

SUMMARY: Karaer K, Rosti RÖ, Torun D, Sanal HT, Bahçe M, Güran Ş. A case with oto-spondylo-mega-epiphyseal-dysplasia (OSMED): the clinical recognition and differential diagnosis. Turk J Pediatr 2011; 53: 346-351.

The oto-spondylo-mega-epiphyseal-dysplasia (OSMED) phenotype is an autosomal recessive trait that is a skeletal dysplasia with the hallmark findings of limb shortening, multiple skeletal and radiological abnormalities, mid-face hypoplasia with a flat nasal bridge, small upturned nasal tip, and sensorineural hearing loss. A 3.5-year-old girl born to consanguineous Turkish parents had characteristic facial features at birth: mid-face hypoplasia, mild hypertelorism, upslanting palpebral fissures, prominent supraorbital ridges, depressed nasal bridge, small upturned nasal tip, long philtrum, and micrognathia. Radiological examination at three years of age revealed large flaring metaphyses and wide flat epiphyses. The humerus and femur showed the characteristic dumbbell shape. She had bilateral hearing loss with no ophthalmologic findings.

There is continuing debate over the clinical overlap and differential diagnosis of OSMED syndrome. The patient was examined considering Weissenbacher-Zweymuller, Stickler type 3, Marshall syndrome, and Kniest dysplasia as possible differential diagnoses. We believe that the presented patient clinically manifested features of OSMED syndrome. We would like to point out that the management of OSMED calls for a coordinated multidisciplinary approach.

Key words: oto-spondylo-mega-epiphyseal-dysplasia (OSMED), short stature, epiphyseal dysplasia, differential diagnosis.

Otospondylomegaepiphyseal dysplasia (OSMED) (MIM 215150) is an autosomal recessive dwarfism disorder characterized by limb shortening, multiple skeletal and radiological abnormalities, mid-face hypoplasia with a flat nasal bridge, small upturned nasal tip, and sensorineural hearing loss. Radiographic findings include short dumbbell-shaped long bones, large epiphyses with metaphyseal flaring, mild platyspondyly, and vertebral coronal clefts[1].

Inborn errors of cartilage collagen formation are due to mutations of the genes controlling the synthesis of type II, type IX, type X, and type XI collagen molecules. Therefore, in the differential diagnosis, cartilage collagen-related disorders Stickler syndrome type 3 (MIM 184840), Weissenbacher-Zweymuller syndrome (WZS) (MIM 277610), Marshall syndrome (MS) (MIM 154780), and Kniest dysplasia (KD) (MIM 156550) merit attention. All of these phenotypes except MS and KD are caused by mutations of the COL11A2 gene[2].

In this report, a Turkish girl with short stature, bilateral sensorineural hearing loss, dysmorphic facial features, and abnormal radiological findings is described. Our OSMED syndrome diagnosis was based on clinical and radiological findings. The differential diagnosis of OSMED syndrome is also discussed.

Case Report

The patient, a 3.5-year-old Turkish girl, was referred to our department due to short stature and bilateral hearing loss. She was

born to healthy first-cousin parents after an uncomplicated pregnancy. There was no exposure to infections, medication or drugs during the pregnancy. Her birth weight was 2360 g (below 3rd centile) and length 44 cm (below 3rd centile); her head circumference was not recorded. The mother was 19 years old and the father was 27 years old at birth. There was no history of this form of dysplasia or hearing loss in the family. Hearing test at the age of 3 showed moderate bilateral sensorineural hearing loss, due to which, at the time of diagnosis, her language development was significantly retarded. Her medical history consisted of a surgical procedure for correction of cleft palate and use of hearing aids.

On her physical examination at 3.5 years of age, her height was 87 cm (below 3rd centile), weight was 11.5 kg (3^{rd} centile) and head circumference was 50 cm (50^{th} centile). There was rhizomelic shortening of the upper and lower extremities. On craniofacial examination, brachycephaly, mid-face hypoplasia, mild hypertelorism, upslanting palpebral fissures, prominent supraorbital ridges, depressed nasal bridge, small upturned nasal tip, long philtrum, high-arched palate, micrognathia, and small teeth were observed (Fig. 1). Generalized brachydactyly with no limitation of joint movements was also noted.

The X-ray examination of the thoracolumbar spine showed mild platyspondyly (Fig. 2). The radiographs demonstrated short long bones (humerus, radius, ulna, femur, tibia, fibula) with large flaring metaphyses and wide flat epiphyses. The humerus and femur showed the characteristic dumbbell shape (Fig. 3). Radiograph of the pelvis showed squared iliac wings and a diastatic appearance of the symphysis pubis (Fig. 4). Radiographs of both hands were unremarkable (Fig. 5).

According to ophthalmologic examination, she had no sign of myopia, retinal detachment or vitreoretinal degeneration.

Complete *blood* count *and* routine biochemistry tests for renal, liver and thyroid function were within normal limits. Chromosome analysis of peripheral leukocytes using high resolution binding technique showed a normal 46, XX female karyotype. No molecular genetic analyses were performed on the COL11A2 gene in this patient.

Discussion

On the basis of the clinical manifestations in our patient, the most compatible diagnosis is OSMED syndrome. To the best of our knowledge, only a few patients with OSMED syndrome

Fig. 1. Frontal and lateral view of the case showing: (a) brachycephaly, mid-face hypoplasia, mild hypertelorism, upslanting palpebral fissures, prominent supraorbital ridges, depressed nasal bridge, snub nose, anteverted nares, long philtrum, high-arched palate, and micrognathia.

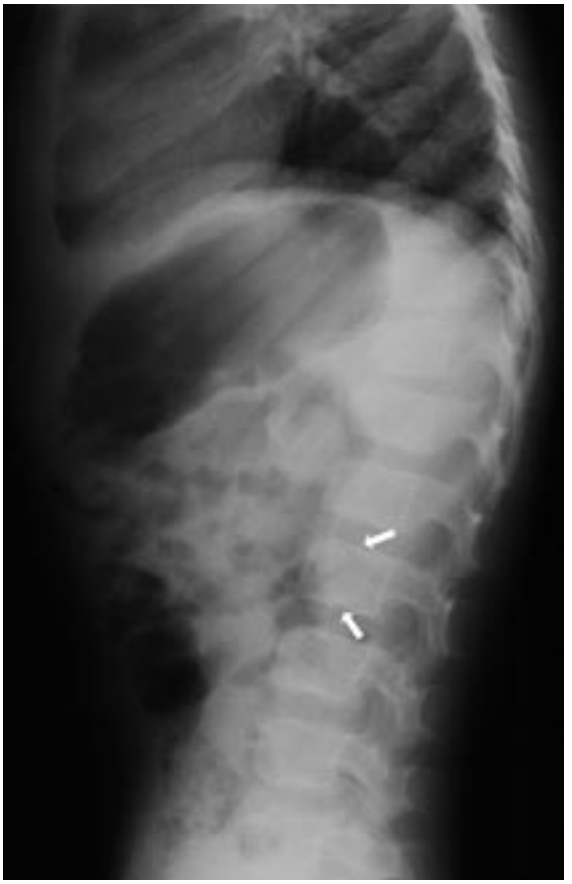

Fig. 2. Lateral radiograph of the thoracolumbar vertebral column showed mild platyspondyly with increased anteroposterior length of the vertebrae and end-plate surface irregularities (arrows).

have been well documented[1,3,4]. A comparison of our patient with the previously presented patients diagnosed as autosomal recessive OSMED showed that the cardinal features of these patients were characteristic face (mid-face hypoplasia with a flat nasal bridge, small upturned nasal tip), cleft palate, sensorineural hearing loss, short stature, and abnormal radiographic findings (dumbbell-shaped femora and humeri, enlarged epiphyses and vertebral platyspondyly). This permits specification of a distinct clinical and radiological phenotype that has to be differentiated from a number of allelic and morphologically similar disorders. These major findings were reported in all families and are present in our case. In addition to these cardinal findings, enlarged joints, short hands and short fingers were common findings in cases with OSMED syndrome, which we also observed in our patient[1]. Moreover, the lack of high myopia and characteristic radiological findings - especially short dumbbell-shaped long bones in later infancy and childhood - are consistent with the diagnosis of OSMED syndrome[5].

The features of OSMED are similar to those of other skeletal disorders: phenotypically related allelic disorders of Stickler syndrome type 3, WZS and non-allelic MS and KD, which constitute a spectrum of clinical severity and inheritance model. The clinical findings of

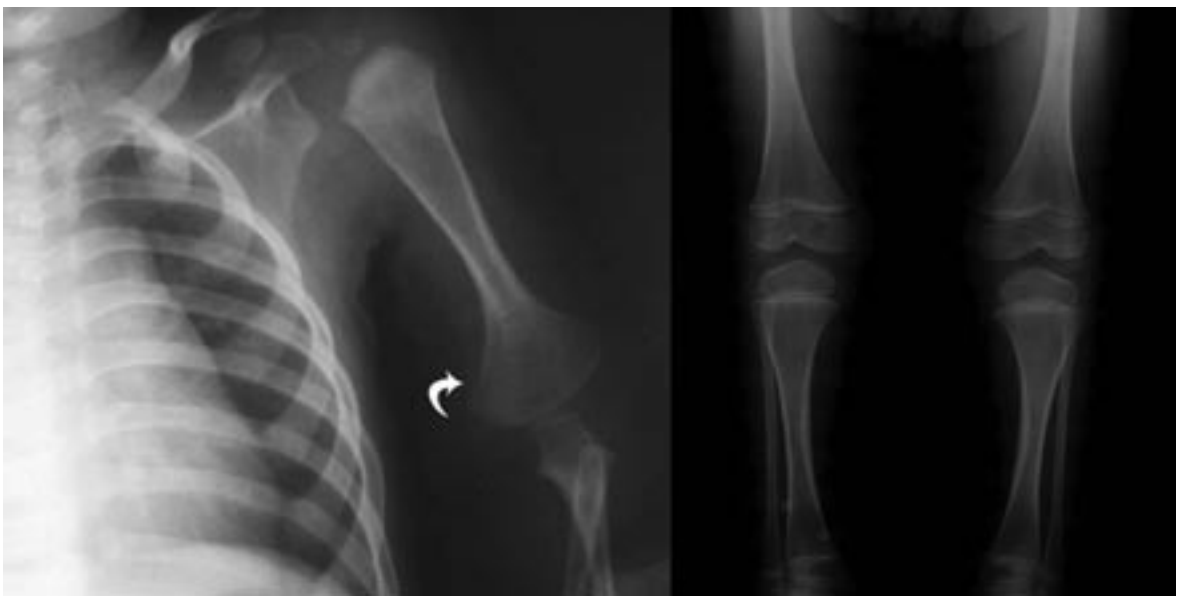

Fig. 3. The anteroposterior radiograph of the left arm. Note that the humerus is short with its flared and large metaphyso-epiphyseal aspect (arrow), giving the bone a 'dumbell' shape.

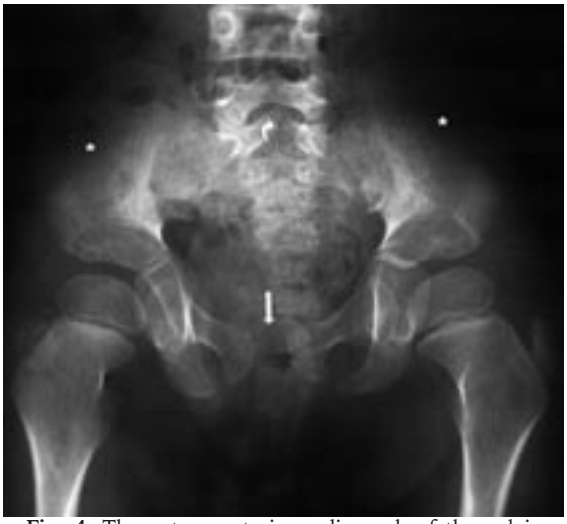

Fig. 4. The anteroposterior radiograph of the pelvis showing slight squared appearance of the iliac wings (stars). There is a wide gap between the two pubic bones at the symphysis pubis joint, which can be designated as 'diastasis' (arrow). The posterior fusion defect at the first sacral vertebra is also seen (curved arrow).

OSMED, Stickler syndrome type 3, WZS, MS, KD and our patient are summarized in Table I. Dysmorphic features and skeletal radiological findings with no ocular symptoms (high myopia, vitreoretinal degeneration, and retinal detachment) are common findings of allelic OSMED, Stickler type 3 and WZS. In contrast, ocular symptoms are observed in non-allelic MS and KD[1]. OSMED, Stickler syndrome type 3 and WZS are caused by different homozygous or heterozygous mutations in the gene encoding collagen type 11, alpha 2 protein (COL11A2), which is localized on human chromosome 6p21.3. In view of such information, the best hypothesis that explains the normal ophthalmologic findings is that COL11A2 is not expressed in the vitreous body[6].

As seen in Table I, OSMED syndrome shows more similarities to WZS. The main clinical features diagnostic of WZS include autosomal dominant inheritance pattern with rhizomelic limb shortening at birth, micrognathia, cleft palate, depressed nasal root, hypertelorism, and protruding eyes. Radiological findings include vertebral coronal clefts, bulbous deformity of ischial and pubic bone, broad iliac wings, enlarged epiphyses, and dumbbell widening of long bone metaphyses, especially femurs and humeri. Enlarged epiphyses are also common findings in WZS and were present in our patient. The distinguishing feature of WZS is normal adult height with catch-up growth after two to three years of age, which is not present in OSMED syndrome and was not seen in our case[2]. Allelic Stickler syndrome type 3 has characteristic facial features of Stickler syndrome type 1 in combination with hearing impairment. Cleft palate or mild arthropathy occurred in several patients, whereas ocular findings of the syndrome were absent. We excluded this syndrome with the absence of rhizomelic dysplasia and short and dumbbell-shaped long bones, which should be present in OSMED syndrome, as were present in our case. Some clinical researchers believe that each of these three disorders is a separate and distinct entity. Others believe that the three represent a spectrum of severity of one disorder. Some researchers have suggested that the name OSMED be used as a general heading that consists of heterozygous OSMED, which encompasses WZS and Stickler syndrome type 3 and is inherited as an autosomal dominant trait, and homozygous OSMED, which encompasses autosomal recessive cases of OSMED[4,7,8].

Phenotypically related autosomal-dominant inherited MS and KD are characterized by short stature, sensorineural hearing loss, and facial findings (flat mid-face, micrognathia, long philtrum), as seen in our patient. Both MS and KD have ocular findings (myopia,

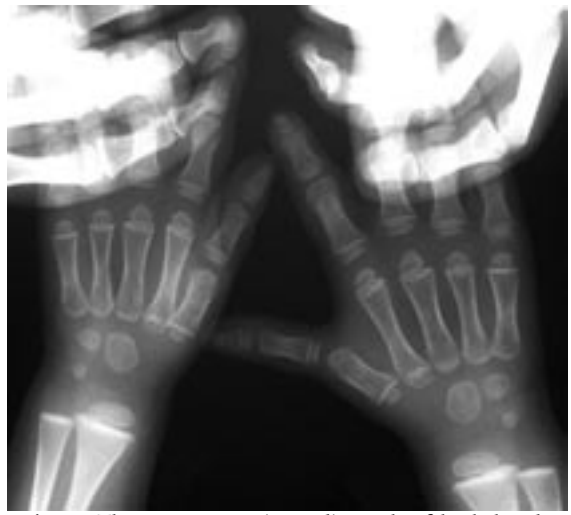

Fig. 5. The anteroposterior radiograph of both hands with normal ossification of the carpal bones and joint spaces.

Table 1. Clinical Differentiation of the Reported Case with OSMED in Comparison with Other Phenotypically Similar Syndromes

Clinical Features			OSMED	Weisenbacher-Zweimuller Syndrome (WZS)	Stickler Syndrome type 3	Marshall Syndrome (MS)	Kniest Dysplasia	Our Case
Inheritance	-		AR	AD	AD	AD	AD	AR
Growth	Height	Short stature	+	-	-	+	+	+
Head and neck	Face	Mid-face hypoplasia	+	+	+	+	+	+
		Long philtrum	+	+	+	+	+	+
		Small jaw	+	+	+	+	+	+
	Ears	Sensorineural hearing loss	+	+	+	+	+	+
	Eyes	No ocular	+	+	+	-	-	+
		Ocular Symptoms •Myopia •Congenital cataracts •Esotropia •Retinal detachment •Glaucoma	-	-	-	+	+	-
	Nose	Anteverted nares	+	+	+	+	+	+
		Short nose	+	+	+	+	+	+
	Mouth	Pierre-Robin sequence	+	+	+	+	+	+
		Cleft palate	+	+	+	+	+	+
		Prominent, protruding upper incisors	-	-	-	+	-	-
Skeletal	Spine	Vertebral coronal clefts	+	+	-	-	+	+
		Mild platyspondyly	+	+	-	+	+	-
	Pelvis	Bulbous deformity	-	-	-	+	+	-
		of ischial and pubic bone Broad iliac wings	+	+	-	-	-	+
	Limbs	Rhizomelic limb shortening (infancy)	+	+	-	+	+	+
		Dumbbell widening of long bone metaphyses, especially femurs and humeri	+	+	-	-	+	+
		Enlarged epiphyses	+	+	-	-	+	+
		Metaphyseal flaring	+	+	-	-	-	+
		Prominent IP joints	+	+	-	-	+	+
		Short hands and fingers	+	+	-	-	+	+

AD: Autosomal dominant. AR: Autosomal recessive. IP: Interphalangeal.

congenital cataracts, esotropia, retinal detachment, glaucoma), whereas our patient has none. The other differentiating feature of MS is the presence of limited mobility of the metacarpophalangeal joints and, possibly, the greater involvement of the vertebral bodies[9]. The long bone changes are similar to those found in OSMED syndrome, which is probably not separate from the MS presented in Table I. Furthermore, patients with KD have very short stature and marked spinal changes, which are less obvious in OSMED.

As a very rare syndrome, the diagnosis of OSMED is an important clinical step to manage the normal development of the patients. For example, in our case, speech delay was due to bilateral hearing loss. The phenotypic expression of OSMED is described in our paper to help clinicians diagnose the patients in the early phases of development. Although there is no specific treatment of OSMED, diagnosing the syndrome in early phases may help the normal development of the patients, and a coordinated multidisciplinary approach is desirable to achieve this goal. Genetic counseling may be of benefit for affected individuals and their families. Another goal of this presentation is for this information to be analyzed together with other patients in the future, which will assist in clarifying the phenotype of the OSMED syndrome.

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