

## LETTER TO JMG

# Clinical, radiological, and chondro-osseous findings in opsismodysplasia: survey of a series of 12 unreported cases

V Cormier-Daire, A L Delezoide, N Philip, P Marcorelles, K Casas, Y Hillion, L Faivre, D L Rimoin, A Munnich, P Maroteaux, M Le Merrer

*J Med Genet* 2003;40:195–200

Opsismodysplasia (*opsimos* in Greek = late) is a rare chondrodysplasia, first described in 1977 by Zonana *et al*<sup>1</sup> as a unique chondrodysplasia and designated “opsismodysplasia” only in 1984.<sup>2</sup> The disorder is characterised clinically by micromelia with extremely short hands and feet and respiratory distress responsible for death in the first few years of life.<sup>2</sup> The main radiological features include severe platyspondyly, major delay in skeletal ossification, and metaphyseal cupping. To date, 13 cases have been reported and recurrence in sibs and/or consanguinity have suggested an autosomal recessive mode of inheritance.<sup>1–6</sup> Here, we describe the clinical, radiological and chondro-osseous findings of 12 previously unreported cases in nine families. We show that opsismodysplasia is not a consistently lethal condition and we identify the severity of the delayed bone ossification as an important feature, distinct from other forms of spondylo(epi)metaphyseal dysplasias.

## PATIENTS AND METHODS

Seven male and five female cases originating from nine families of French (4/9), German, (1/9), and Algerian origin (4/9) were included in the study. All affected cases presented with the following inclusion criteria: (1) major delay in epiphyseal ossification, (2) platyspondyly, (3) metaphyseal cupping, and (4) very short metacarpals and phalanges. Half of the cases were prenatally diagnosed during ultrasound follow up of the pregnancies and half of them were diagnosed postnatally. Pregnancies were terminated between 15 and 29 weeks' of gestation. For chondro-osseous studies, the samples were

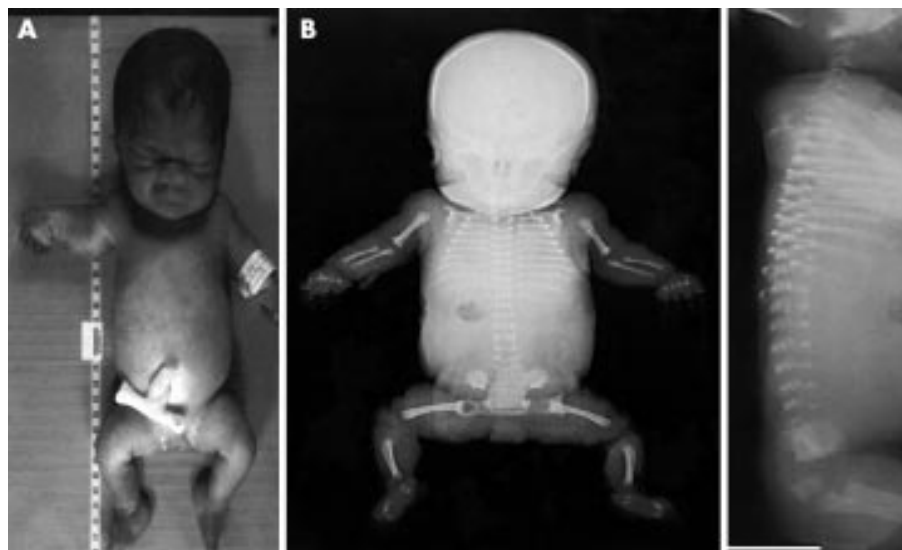
## Key points

- We present the clinical, radiographic, and histological findings of 11 new cases of opsismodysplasia belonging to eight families.
- All cases presented with dysmorphic features, large anterior fontanelle, short hands and feet, and short stature. Radiographic features included very delayed bone maturation, marked shortness of the hand and foot bones with metaphyseal cupping and thin vertebral bodies.
- The outcome was variable and five children are still alive. They all have short stature, dorsolumbar scoliosis, and coxa valga.
- Recurrence in sibs and consanguinity are highly suggestive of an autosomal recessive mode of inheritance.

embedded in paraffin and HES routinely stained after fixation in 4% formaldehyde and decalcification with EDTA.

## RESULTS

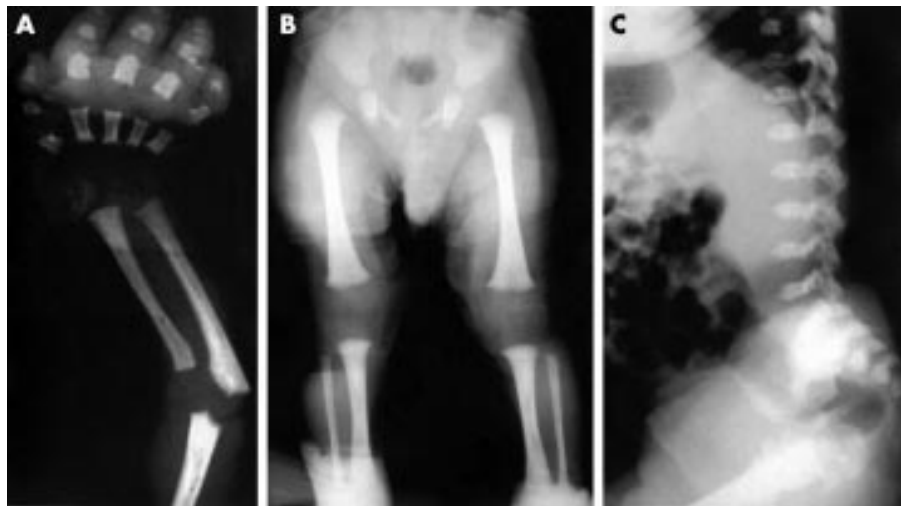
Table 1 summarises the clinical features of the 12 novel cases of opsismodysplasias. In 8/12 cases, ultrasound showed shortness of the long bones and short extremities in early pregnancy (14–24 weeks' gestation). Head circumference was consistently in the normal range. A depressed nasal bridge



**Figure 1** Clinical (A) and radiological findings (B) in case 3 (29 weeks' gestation) Note the very short limbs and hands, depressed nasal bridge (A), hypoplastic vertebral bodies, very short metacarpals, horizontal acetabular roof, and metaphyseal irregularities (B).



**Figure 2** Facial features in cases 8 (A), 9 (B), 10 (C at 1 year and D at 5 years), and 12 (E). Note the frontal bossing, depressed nasal bridge, and short nose.



**Figure 3** X ray findings in case 9 at birth. Note the very short metacarpals and squared middle phalanges (A), the short long bones with absence of the epiphyseal centre around the knee (B), and severe platyspondyly (C).

was noted in 4/12, narrow thorax in 4/12, and cystic hygroma in 2/12 fetuses. The pregnancies were terminated between 14 and 29 weeks in 6/12 cases. Necropsy of the affected fetuses confirmed a coarse face, high forehead, and a short nose with depressed nasal bridge (fig 1A) and radiographs showed hypoplastic vertebral bodies, very short long bones, horizontal acetabular roofs with lateral spurs, and extremely short metacarpals (fig 1B). In 4/12 cases, prenatal evaluation of the pregnancy was considered “normal” but at least three of these cases did not have adequate prenatal assessment.

The other six cases were diagnosed after birth. Birth length was normal in 3/6 cases. Head circumference was in the normal range in 6/6 cases. Other consistent features included large anterior fontanelle, frontal bossing, depressed nasal bridge, short nose, long philtrum, posteriorly rotated ears (fig 2), and short hands and feet.

Among the six neonatal cases, one child died at 3 months of age of respiratory distress already present at birth. The other five children are still alive and are aged 28 months to 15 years. All have short stature (below  $-3-6$  SD), dorsolumbar scoliosis,

and varus deformity of the lower legs. In addition, 3/5 had recurrent respiratory infections and one has recurrent otitis media. All five children have normal cognitive development, but one has motor delay (case 8).

Radiographic findings included extremely short hands and feet with very short and squared metacarpals and phalanges, hypoplastic and flat vertebral bodies, a major delay in epiphyseal ossification, especially in the knee, and metaphyseal irregularity with metaphyseal cupping (figs 3-8). X ray follow up of the survivors showed persistence of an extremely delayed epiphyseal ossification with dysplastic carpal ossification, major shortness of the metacarpals, and metaphyseal irregularities in the knee.

Histopathological examination of fetal bones and cartilage showed wide and numerous epiphyseal vascular canals (fig 9A-C). Chondrocyte density in the resting cartilage was increased, many cells were arranged in clusters, and some of them were ballooned (fig 9D-F). At the growth plate level, the proliferative zone was very disorganised, with a nearly absent columnar organisation. The mineralised matrix trabeculae

**Table 1** Clinical manifestations in 12 novel cases of opsismodysplasia

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12
Ethnic origin	French		French		French	French	Algerian	German	French	Algerian	Algerian	Algerian
Consanguineous parents	–	–	–	–	–	–	+	–	–	+	+	+
Recurrence in sibs	+	Case 1 sib	+	Case 3 sib	–	Case 9 sib	+	–	Case 6 sib	–	–	+
Karyotype	46,XY	46,XX	46,XY	45,XO	46,XX	46,XY	46,XY	46,XX	46,XY	46,XY	46,XX	46,XX
Prenatal findings	Short femora (24 w) Narrow thorax Short hands	IUGR (15 w) Hygroma	IUGR (24 w) Narrow thorax Short hands	IUGR (14 w) Hygroma	Short femora (24 w) Narrow thorax Short hands and feet	Short femora (22 w) Narrow thorax Short hands	–	Polyhydramnios Increased OFC Short femora	–	–	–	–
Birth length	?	?	33 cm (29 w)	9.5 cm (14 w)	31 cm (29 w)	25.5 cm (22 w)	49 cm	45.5 cm	49 cm	48 cm	47.5 cm	46 cm
Birth weight	?	?	1280 g	30 g	1400 g	440 g	2370 g	?	3400 g	3245 g	3260 g	?
Birth OFC	?	?	29 cm	8 cm	29 cm	19.5 cm	35 cm	?	36 cm	?	36 cm	?
Large anterior fontanelle	?	?	+	?	+	+	+	+	+	+	+	+
Dysmorphic features	+	+	+	+	+	+	+	+	+	+	+	+
Coarse face	?	?	+	?	?	?	+	+	+	+	+	+
High forehead	+	?	+	+	?	?	+	+	+	+	+	+
Short nose	+	?	+	+	+	+	+	+	+	+	+	+
Long philtrum	?	?	+	?	+	+	+	+	+	+	+	+
Thin upper lip	?	?	–	?	+	?	+	+	+	+	+	+
Abnormal ears	+	?	–	?	+	?	+	–	+	+	+	+
Respiratory insufficiency												
Pulmonary hypoplasia	?	?	+	?	+	+	+	+	+	–	–	–
Short hands, feet	+	+	+	+	+	+	+	+	+	+	+	+
Psychomotor development	–	–	–	–	–	–	Hypotonia	Motor delay, normal cognitive development	Normal	Normal	Normal	Normal
Malformations	–	–	–	–	–	–	Septal defect	Persistent ductus arteriosus	Ureteral anomaly	–	–	–
Outcome	Termination of pregnancy (24 w)	Termination of pregnancy (15 w)	Termination of pregnancy (29 w)	Termination of pregnancy (14 w)	Termination of pregnancy (29 w)	Termination of pregnancy (22 w)	Death (3 mth) respiratory distress	28 mth Stature <–7 SD Scoliosis Coxa valga	11 y Stature <–3.5 SD Scoliosis Limbs: varus incurvation	11 y Stature <–3 SD Limbs: varus incurvation scoliosis	15 y Stature <–5 SD Scoliosis Bowed legs	15 ys Stature <–5 SD Scoliosis Bowed legs Coxa valga



**Figure 4** X ray findings in case 9 at 16 months of age. Note the short metacarpals with metaphyseal cupping (A), severe epiphyseal delay and metaphyseal flaring (B), and flat vertebral bodies (C).

were thick and irregular (fig 9G-I). These anomalies were observed in all cases but varied markedly in severity among cases, thus paralleling the variability of the x ray manifestations.

## DISCUSSION

Here, we describe the clinical and pathological features of 12 hitherto unreported cases of opsismodysplasia. We first show that opsismodysplasia is not consistently lethal in the neonatal period. Indeed, among the six newborns, only one died in the first year of life of respiratory insufficiency and the other five children are still alive. The combination of our series with previously reported cases (total 25 cases) shows that the outcome is quite variable.<sup>1-7</sup> In fact, apart from 7/24 terminated pregnancies, 7/17 children died of respiratory insufficiency in infancy (<2 years), but 10/17 are still alive and 4/17 are older than 8 years. Long term follow up showed that all children had short stature (<-3 SD) and severe orthopaedic complications dominated by scoliosis and lower limb valgus deformities. Cognitive development was normal.

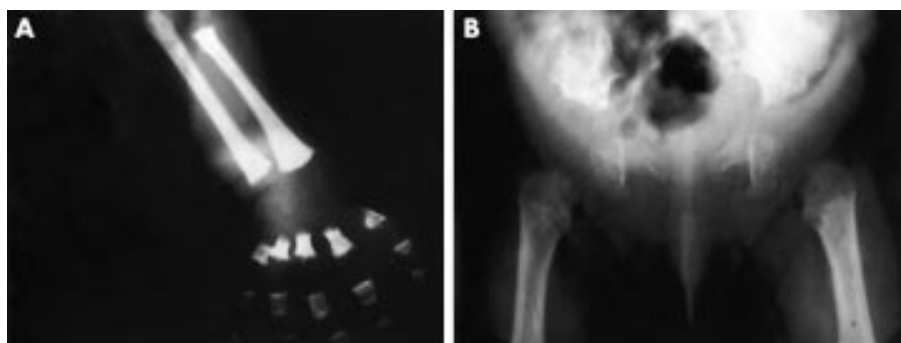
Wide variability in the severity of radiological manifestations was also observed in our series, especially in the prenatal



**Figure 5** X ray findings in case 9 at 5 years of age. Note the dysplastic carpal ossification and the severe shortness of the metacarpals (A), the coxa vara and metaphyseal cupping around the knee (B), and scoliosis (C).

group. This feature led to some overlap with other conditions belonging to the group of lethal platyspondylic chondrodysplasias, particularly spondylometaphyseal dysplasia, Sedhagatyan type. Common features with this condition include short hands, platyspondyly, delayed epiphyseal ossification, metaphyseal cupping, small chest, severe outcome, and autosomal recessive inheritance. However, distinctive features in the Sedhagatyan disorder include normal intrauterine growth, less severe platyspondyly, lacy iliac crest, long fibula, tarsal bone irregularities, and different chondro-osseous findings.<sup>7-11</sup> Moreover, cardiac arrhythmia and intracranial anomalies, which are a part of the Sedhagatyan disorder, have never been noted in any case of opsismodysplasia. Finally, the extreme ossification delay observed in all opsismodysplasia cases is not present in the Sedhagatyan disorder and is a major distinctive feature.

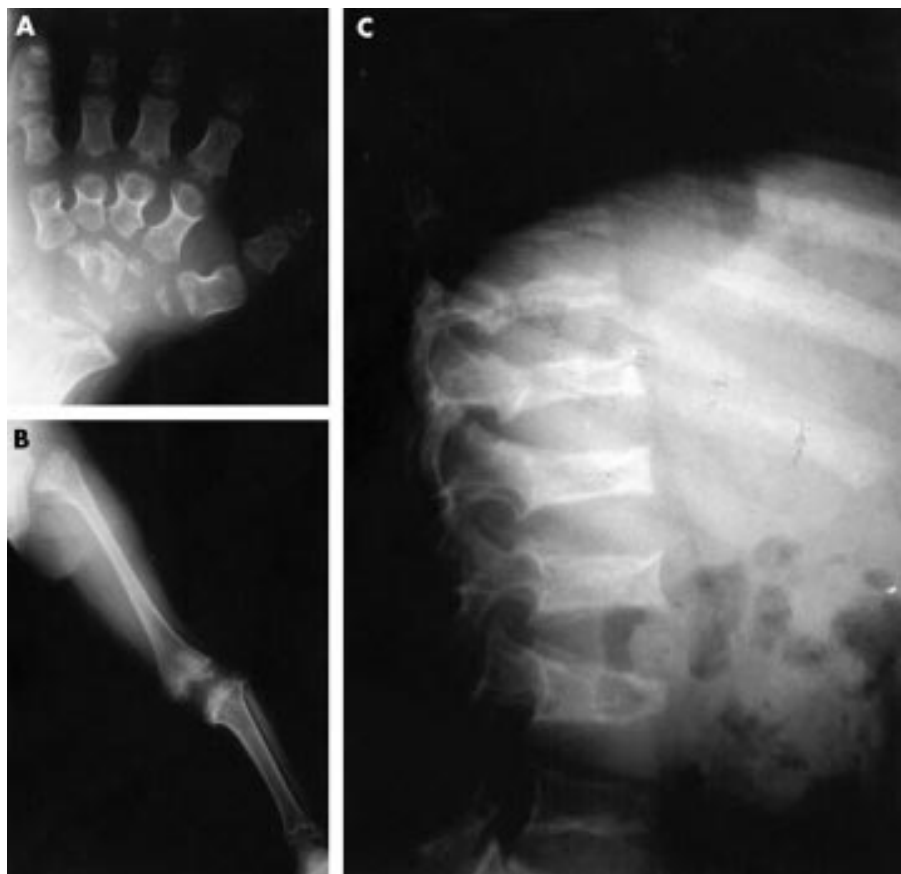
Among a total of 25 cases (16 males and nine females) originating from 17 families (our series and previously reported cases), recurrence in sibs in 4/17 families and consanguinity in 7/17 strongly suggest an autosomal recessive



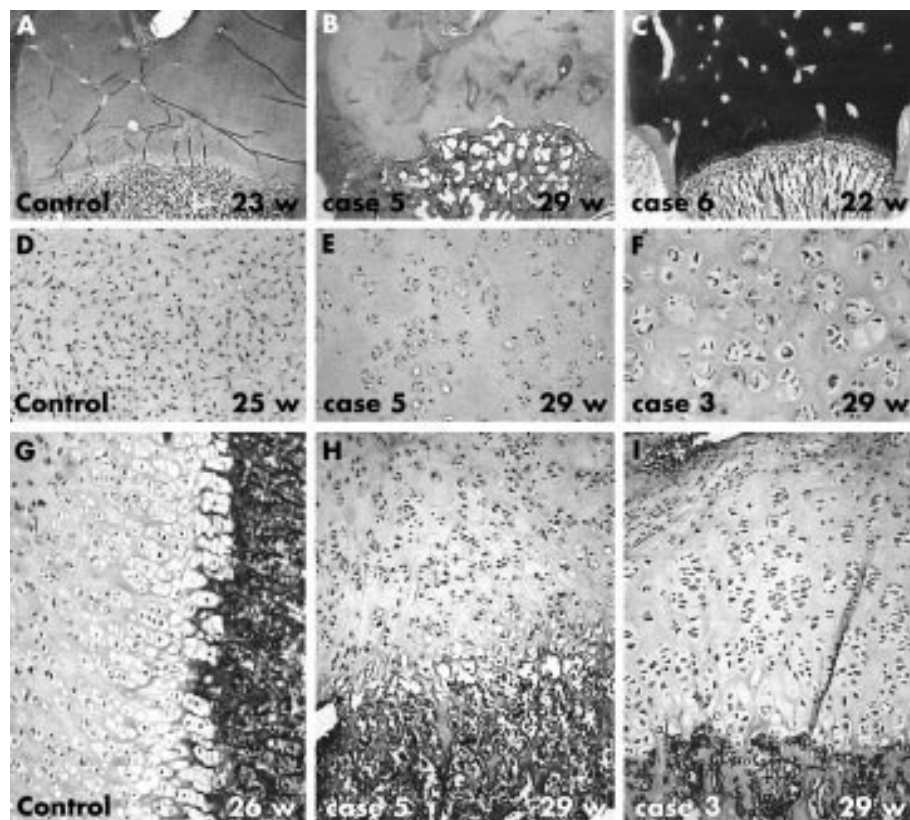
**Figure 6** X ray findings in case 12 at 6 months of age. Note the very short and squared metacarpals (A), the epiphyseal delay, and the irregularity of the femoral neck (B).



**Figure 7** X ray findings in case 12 at 5 years of age. Note the dysplastic carpal ossification (A), the severe metaphyseal changes in the knee (B), and the flat vertebral bodies with anterior beaking (C).



**Figure 8** X ray findings in case 12 at 16 years of age. Note the severity of the metacarpal shortness and the small epiphyses (A), the dislocation of the knee with epiphyseal and metaphyseal changes (B), and the flat and rectangular vertebral bodies (C).



**Figure 9** Histological findings in the fetal cases. (A-C) Frontal section of the femoral head. Comparison of a control fetus (A, 23 week pregnancy) with two cases of opisismodysplasia (B, case 5 and C, case 7). Note the thick primary osseous trabeculae and the enlarged vascular canals. (D-F) Higher magnification of the epiphyseal resting in cases 5 (E), 3 (F), and in an age matched control (D). Note the clusters of ballooned chondrocytes. (G-I) Growth plate at the femoral head site in cases 5 (H), 3 (I), and in an age matched control (G). Note the nearly absent columnar organisation.

mode of inheritance. No gene has yet been identified, but the high degree of consanguinity should allow linkage analysis based on the homozygosity mapping strategy.

In conclusion, opisismodysplasia is a severe distinctive spondylo(epi)metaphyseal dysplasia not consistently lethal in the first years of life, and characterised by major delay in epiphyseal ossification. Future genetic studies will hopefully help to delineate the molecular basis of this rare bone dysplasia and elucidate the mechanism of its clinical variability.

#### ACKNOWLEDGEMENTS

We thank Ralph S Lachman for his helpful comments.

#### Authors' affiliations

**V Cormier-Daire, L Faivre, A Munnich, P Maroteaux, M Le Merrer,** Department of Medical Genetics and INSERM U393, Hôpital Necker, Paris, France

**A L Delezoide,** Service de Biologie du Développement, Hôpital Robert Debré, Paris, France

**N Philip,** Département de Génétique Médicale, Hôpital de La Timone, Marseille, France

**P Marcocelles,** Service d'Anatomie Pathologique, Hôpital Morvan, Brest, France

Correspondence to: Dr V Cormier-Daire, Department of Medical Genetics, Hôpital Necker Enfants Malades, 149 rue de Sèvres, 75015 Paris, France; [cormier@necker.fr](mailto:cormier@necker.fr)

#### REFERENCES

- 1 **Zonana J,** Rimoin DL, Lachman RS, Cohen A. A unique chondrodysplasia secondary to a defect in chondro-osseous transformation. *Birth Defects* 1977;**13**(D):155-62.
- 2 **Maroteaux P,** Stanescu V, Stanescu R, Le Marec B, Moraine C, Lejarraga H. Opisismodysplasia: a new type of chondrodysplasia with predominant involvement of the bones of the hand and vertebrae. *Am J Med Genet* 1984;**19**:171-82.
- 3 **Beemer FA,** KS Kozlowski. Additional case of opisismodysplasia supporting autosomal recessive inheritance. *Am J Med Genet* 1994;**49**:344-7.
- 4 **Santos HG,** Saraiva JM. Opisismodysplasia: another case and literature review. *Clin Dysmorphol* 1995;**4**:222-6.
- 5 **Tyler K,** Sarioglu N, Kunze J. Five familial cases of opisismodysplasia substantiate the hypothesis of autosomal recessive inheritance. *Am J Med Genet* 1999;**83**:47-52.
- 6 **Zeman J,** Baxova A, Houstkova H, Kozlowski K. Opisismodysplasia: a case report. *Australas Radiol* 1997;**41**:35-7.
- 7 **Opitz JM,** Spranger JW, Stoss HR, Pesch HJ, Azadeh B. Sedhagatian congenital lethal metaphyseal dysplasia-observations in a second Iranian family and histopathologic studies. *Am J Med Genet* 1987;**26**:583-90.
- 8 **Peeden JN,** Rimoin DL, Lachman RS, Dyer ML, Gerard D, Gruber HE. Spondylometaphyseal dysplasia, Sedhagatian type. *Am J Med Genet* 1992;**44**:651-6.
- 9 **Elcioglu N,** Hall CM. Spondylometaphyseal dysplasia - Sedhagatian type. *Am J Med Genet* 1998;**76**:410-14.
- 10 **Ker B,** Smith V, Patel R, Ladusans E, Silence DO. Spondylometaphyseal dysplasia Sedhagatian type associated with lethal arrhythmia and normal intrauterine growth in three siblings. *Clin Dysmorphol* 2000;**9**:167-72.
- 11 **Koutouby A,** Habibullah J, Mainuddin FA. Spondylometaphyseal dysplasia: Sedhagatian type. *Am J Med Genet* 2000;**90**:199-202.