

- <sup>6</sup> Jeffreys AJ, Wilson V, Thein SW. Hypervariable "minisatellite" regions in human DNA. *Nature* 1985;314:67-73.
- <sup>7</sup> Watkins PC, Tanzi RE, Gibbons KT, *et al.* Isolation of polymorphic DNA segments from human chromosome 21. *Nucleic Acids Res* 1985;13:6075-88.
- <sup>8</sup> Crandall BF, Weber F, Muller HM, Burwell JK. Identification of 21r and 22r chromosomes by quinacrine fluorescence. *Clin Genet* 1972;3:264-70.
- <sup>9</sup> De Grouchy J, Turleau C. *Clinical atlas of human chromosomes*. 2nd ed. New York: John Wiley, 1984:350-4.

- <sup>10</sup> Kazazian HH, Antonarakis SE, Wong C, *et al.* Ring chromosome 21: characterisation of DNA sequences at sites of breakage and reunion. *Ann NY Acad Sci* 1985;450:33-42.

Correspondence and requests for reprints to Dr I D Young, Department of Child Health, Clinical Sciences Building, Leicester Royal Infirmary, PO Box 65, Leicester LE2 7LX.

## Is geroderma osteodysplastica underdiagnosed?

A G W HUNTER

*Division of Genetics, Children's Hospital of Eastern Ontario, and University of Ottawa, 401 Smyth Road, Ottawa, Ontario, Canada K1H 8L1.*

**SUMMARY** A girl with mild geroderma osteodysplastica is reported in order to raise the profile of this autosomal recessive condition which may be underdiagnosed. The important signs of this syndrome include a droopy, jowly face with a degree of malar hypoplasia and mandibular prognathism, lax, but non-hyperelastic skin, most marked over the extremities, and osteoporosis which may be associated with fractures and vertebral collapse.

Patients with geroderma osteodysplastica (GO) look older than their chronological age because of congenital lax skin with decreased elastic recoil, which gives them a droopy, jowly appearance. Joint hyperextensibility, most marked in the metacarpophalangeal joints, and a generalised osteoporosis are important associated findings. The latter is often accompanied by susceptibility to bone fractures, including vertebral compression, with a decreased upper/lower body segment ratio. The term GO was first used to describe an extended Swiss family that was the subject of a number of reports.<sup>1,2</sup> The inheritance was originally reported as X linked recessive because three affected branches of the family were connected through unaffected women. However, autosomal recessive inheritance is now accepted because males and females in the original family were involved with equal severity, and there was a high level of consanguinity in the region.<sup>3</sup> Furthermore, the two families reported by Hunter *et al*<sup>3</sup> are best explained on that basis. Only one additional family has been reported,<sup>4</sup> but other

patients who may have had this condition have been considered to have different diagnoses.<sup>5,6</sup> This paper describes a French Canadian girl who is mildly affected with GO, in the hope that the report will raise the profile of this condition, which may be under-recognised.

### Case report

The proband was the only child of a healthy, unrelated French Canadian couple. Her maternal half sib required surgery for congenital heart disease but was otherwise well, and three maternal first cousins once removed had died of a mucopolysaccharidosis. The pregnancy had been complicated by threatened labour at 32 weeks, which led to bed rest until delivery at 38 weeks. At birth she weighed 1760 g and was noted to have lax skin with the veins showing through. Her early childhood was uncomplicated, although she bruised easily and had delayed motor milestones. She was having difficulty in grade one and suffering headaches and abdominal pain on school days. During investigation of her school problems a diagnosis of Ehlers-Danlos syndrome had been made, and she was referred to the genetics clinic by her private physician.

On examination at the age of six years six months, she was a shy, cooperative child who was 116 cm tall (50th centile), weighed 21 kg (50 centile), and had an OFC of 49.1 cm (25th centile). Her upper:lower segment ratio was 0.81 (checked on separate days), suggesting a short trunk (fig 1). Her hair pattern, distribution, and structure was normal. Her ears were in the normal position, had a normal shape, and were not hyperelastic. She had a long, square face with significant malar hypoplasia and mandibular prognathism (fig 2). The eyes were grey-blue with occasional Brushfield spots; the inner canthal

distance was 2.6 cm and the outer 7.2 cm. There was some droopiness to the lower eyelids and eversion of the lower lip. Her teeth were crowded and had normal lucency.

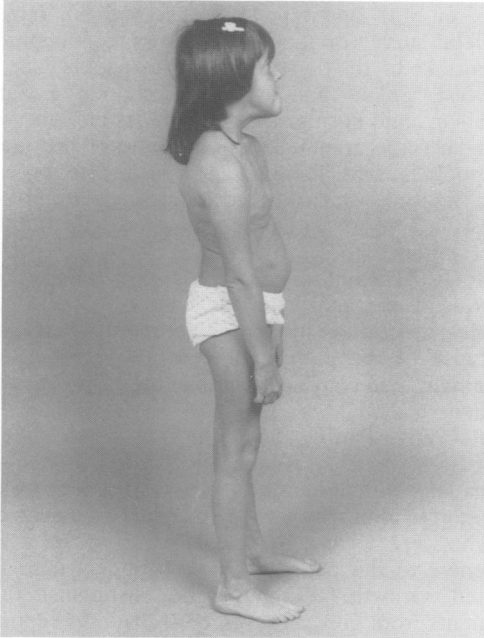


FIG1 Lateral view of the patient at six years six months showing apparent short trunk, mandibular prognathism, and some skin laxity.



FIG2 Photograph of patient showing long, square face, jowly cheeks, maxillary hypoplasia, mandibular prognathism, and slight eversion of the lower eyelids.

The truncal skin was slightly droopy and the nipples were inverted. There was a bruise on the trunk and several on the legs. There was generalised joint hyperextensibility, most marked at the shoulders, elbows, knees, and small joints of the fingers, which could be readily folded around one another. The skin of the dorsum of the hands and feet was lax and lagged in place when drawn up in a tent (fig 3). It was not hyperelastic and there was no unusual scarring; the veins were generally visible. She had flat feet.



FIG3 Dorsum of patient's hand showing general skin laxity and decreased elasticity, in that the skin remained tented when pulled up.

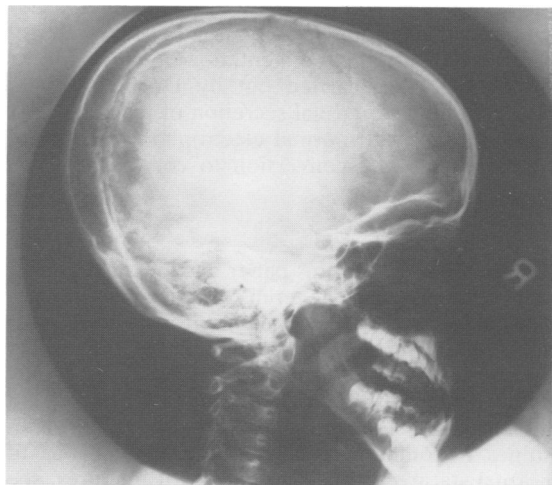


FIG4 Skull radiograph showing wormian bones and long slender mandible with an underbite.

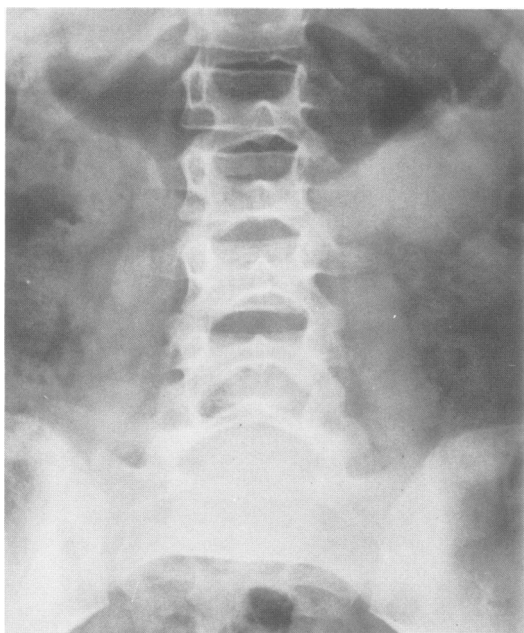


FIG 5 Radiograph of the lower spine. The photograph was taken to emphasise the bones, but shows little contrast between the osteoporotic vertebral bodies and surrounding soft tissue.

Radiographs of the skull showed a normal configuration with numerous wormian bones in the lambdoid sutures. The body of the mandible was long and slender and produced an underbite (fig 4). There was mild osteoporosis of the spine (fig 5) and the long bones were spindly and undermineralised. Electron microscopic examination of a skin biopsy showed non-specific fragmentation of elastic fibres. Collagen studies carried out by Dr Peter Byers (Seattle) showed normal secretion of type I and III procollagens, with normal electrophoretic mobility of the chains and conversion to collagen.

## Discussion

The girl reported in this paper has the appearance, skin findings, and generalised joint hyperextensibility and osteoporosis compatible with the diagnosis of GO. Intra- and interfamilial variability in severity of the condition has been noted, especially with respect to the susceptibility to fractures and alterations in stature.<sup>1-4</sup> Delay in early motor milestones is common. Although our patient was of normal stature and had no history of fractures, she had osteoporosis and a reduced upper/lower segment ratio, characteristic mandibular prognathism,

and thin alveolar bone. Her school problems were, at least in part, a situational reaction to teasing and have improved.

In the absence of a history of susceptibility to fractures or joint complications, it is likely that most children with apparent cutis laxa will not have a skeletal survey or that mild osteoporosis might be overlooked. In that regard two papers are of interest. Sakati and Nyhan<sup>5</sup> described a Saudi Arabian child born to consanguineous parents, who had lax skin, joint laxity, especially of the metacarpophalangeal joints, generalised osteoporosis, and multiple fractures, including vertebral compression. No photograph was provided, but the description of the facies was certainly compatible with GO. The authors did discuss GO but appeared to rule it out, partly on the basis of some of the clinical description in the original report, but mainly because of the pattern of inheritance which had originally been proposed. It seems likely that the patient had GO.

Recently, Patton *et al*<sup>6</sup> reported seven patients from five families, under the title of 'Congenital cutis laxa with retardation of growth and development'. No photographs were provided of cases 5 and 6 who were noted to have osteoporosis, and whose likeness to the patient of Sakati and Nyhan<sup>5</sup> was noted. Growth failure does not distinguish these patients from GO, as seven of 14 patients reported with GO have been below the 3rd centile in height. There is also doubt as to the significance of developmental delay as a distinguishing feature. Most of the cases of Patton *et al*<sup>6</sup> were young when reported and delayed motor milestones are not unexpected given the degree of joint laxity. A degree of global developmental delay has also been an occasional finding in GO.<sup>3</sup>

Therefore, the diagnosis of GO should be considered in any person with congenital cutis laxa, especially when it is most marked in the acral regions, and is accompanied by visually prominent veins, joint laxity, and compatible facial features. Significant variability in skeletal manifestations is to be expected and the skeletal survey must be assessed carefully.

## References

- 1 Bamatter F, Franceschetti A, Klein D, Sierro A. Gérodermie ostéodysplasique héréditaire. *Ann Pediatr (Paris)* 1950;174:126-7.
- 2 Boreaux G. La gérodermie ostéodysplasique à hérédité liée au sexe, nouvelle entité clinique et génétique. *J Genet Hum* 1969;17:137-8.
- 3 Hunter AGW, Martsolf JT, Baker CG, Reed MH. Geroderma osteodysplastica: a report of two affected families. *Hum Genet* 1978;40:311-24.
- 4 Lisker R, Hernandez A, Martinez-Lavin M, *et al*. Geroderma osteodysplastica hereditaria: report of three affected brothers and literature review. *Am J Med Genet* 1979;3:389-95.

- <sup>5</sup> Sakati NO, Nyhan WL. Congenital cutis laxa and osteoporosis. *Am J Dis Child* 1983;137:452-4.
- <sup>6</sup> Patton MA, Tolmie J, Ruthnum P, Bamforth S, Baraitser M, Pembrey M. Congenital cutis laxa with retardation of growth and development. *J Med Genet* 1987;24:556-61.

Correspondence and requests for reprints to Dr A G W Hunter, Division of Genetics, Children's Hospital of Eastern Ontario, 401 Smyth Road, Ottawa, Ontario, Canada K1H 8L1.

## Achondroplasia in sibs of normal parents

N PHILIP, M AUGER, J F MATTEI, AND F GIRAUD

*Centre de Génétique Médicale et INSERM U242, Hôpital d'Enfants de la Timone, Boulevard Jean Moulin, 13385 Marseille Cedex 5, France.*

**SUMMARY** A new case of recurrent achondroplasia in sibs of normal parents is reported. Two sisters and a half sister were affected. Various mechanisms can be postulated to account for unexpected recurrence of achondroplasia in the same sibship. Germinal mosaicism and unstable premutation are discussed here.

Achondroplasia is the commonest type of short limbed dwarfism. Dominant inheritance is clearly established and sporadic cases are the result of new mutations. Three families with more than one affected sib and normal parents have been previously reported. In the present report, a normal father had three achondroplastic daughters from two different mothers.

### Case reports

The family pedigree is shown in fig 1. Case 1 (II.1) was born in 1975 to a healthy, unrelated 17 year old mother and 30 year old father. Birth length was 47.5

cm and birth weight 3030 g. Achondroplasia with rhizomelic shortening of the limbs and macrocephaly was suspected at birth and x ray films of the skeleton confirmed the diagnosis. When examined for the second time, the girl was 12 years old and 116 cm tall. Psychomotor development was normal. Clinical and radiological features were typical of achondroplasia. A normal boy was born in 1977.

Case 2 (II.3), born in 1981, is the sister of case 1. The diagnosis of achondroplasia was immediately evident. At five years of age, she was 85 cm tall.

Both parents were examined. Clinical and radiological examination was normal with no stigmata of achondroplasia.

Case 3 (II.4) is the half sister of cases 1 and 2, with

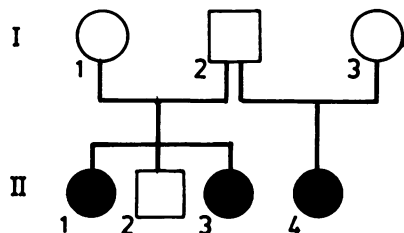


FIG 1 Pedigree of family.

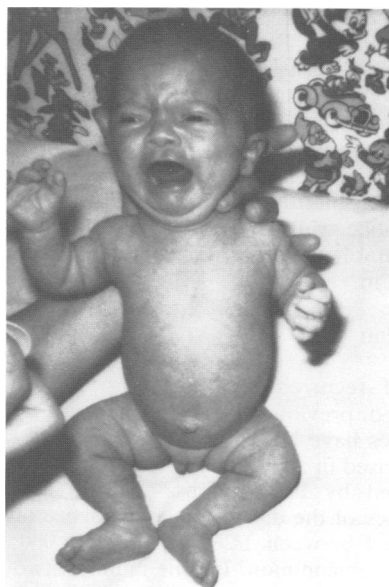


FIG 2 Case 3 at birth.