Abstract

We report a 6 year old boy with multiple fractures owing to bilateral, peculiar, wave-like defects of the tibial corticalis with alternative hyperostosis and thinning. Furthermore, he had Wormian bones of the skull, dentinogenesis imperfecta, and a distinct facial phenotype with hypertelorism and periorbital fullness. Collagen studies showed normal results. His sister, aged 2 years, showed the same facial phenotype and dental abnormalities as well as Wormian bones, but no radiographical abnormalities of the tubular bones so far. The mother also had dentine abnormalities but no skeletal abnormalities on x ray. This entity is probably the same as described in a sporadic case by Suarez and Stickler in 1974. In spite of the considerable overlap with osteogenesis imperfecta (bone fragility, Wormian bones, and dentinogenesis imperfecta), we believe this disorder to be a different entity, in particular because of the unique cortical defects, missing osteopenia, and normal results of collagen studies.

Keywords: dentinogenesis imperfecta; multiple fractures; osteogenesis imperfecta; skeletal dysplasia

In 1974, Suarez and Stickler reported a sporadic patient with a skeletal dysplasia characterised in particular by unique cortical lesions of the long bones and Wormian bones of the skull. We describe two sibs with a very similar constellation of skeletal abnormalities and discuss the differential diagnosis.

Case reports

Patient 1 was born at term as the first child of Dutch, non-consanguineous parents. Birth weight was 3300 g and length 50 cm. A haemangioma was noted on his left upper arm. He sat unsupported and walked at the ages of 12 and 18 months, respectively. His mental development was normal. He had three episodes of tibial fracture each following minor trauma, two affecting the right (at 4 and 6 years of age) and one the left tibia (at 5 years of age). They were all treated with a cast. Furthermore, ordinary contusions and bruising seemed to be remarkably painful to him.
On examination at the age of 6½ years, his height was 113.5 cm (3rd centile) and his weight 20 kg (50th centile). OFC was 53 cm (75th centile) and the skull was dolicchocephalic. He showed hypertelorism (ICD 3.3 cm, +2 SD) and orbital fullness (fig 1). His teeth were translucent; the deciduous teeth were flat, had a yellowish colouration, and were susceptible to caries. His chest was noted to be asymmetrical with a dent on the left. The extension of both elbows was restricted to ±150°. His feet showed evident clinodactyly of the third and fourth toes, respectively, and short fifth rays. On the left upper arm, a haemangioma was present but fading. There was a mild excess of skin which was not hyperelastic. There were no signs of abnormal scarring, skin fragility, or ligamentous laxity. Hearing was normal.

X-ray examination, begun at 4 years of age because of the fractures, showed a peculiar, irregular, wave-like aspect bilaterally of the tibial cortex with alternately localised hyperostosis and cortical thinning (figs 2 and 3). The lesions were more pronounced on the anterior side of the tibiae. One and a half years later, the cortical abnormalities of the tibiae were essentially unchanged. The fractures occurred at sites where the cortex was thin (fig 2). There was also a hypodense lesion of the fibular cortex (fig 2). Furthermore, mild epiphyseal streaking was noted. At the age of 6 years, a small hypodense area was seen radiographically in the cortex of the right femur (fig 4). Radiographs of the long bones of the upper limbs and of the hands and feet showed no abnormalities. In particular, no signs of osteolysis were seen. A skull radiograph showed multiple Wormian bones (fig 5). The spine had a normal appearance. The ribs were slender.

Radioactive investigation of the bone mineral density showed increased activity of the proximal metaphyseal-diaphyseal transition of the left tibia according to a fracture at that time, non-homogeneous activity with a patchy appearance in the right tibia, and normal results in the rest of the skeleton.

On investigation, calcium, phosphate, alkaline phosphatases, and vitamin D were normal. Metabolic screening (including serum and urine amino acid chromatography, serum sialotransferrines and steroles, urinary excretion of mucopolysaccharides, oligosaccharides, organic acids, purines, and pyrimidines) showed normal results. Cytogenetic analysis showed a normal 46,XY karyotype.

Electrophoresis of collagen produced by cultured fibroblasts showed normal collagen type I formation and a normal collagen I:III ratio. Polymorphisms in the 3' untranslated region of the COL1A1 and COL1A2 genes were analysed in genomic DNA and cDNA to assess possible null alleles and showed normal expression of the COL1A1 and COL1A2 alleles.

Patient 2 is the younger sister of patient 1 and had had no fractures. Her motor development was slightly retarded and she walked at 19 months. On examination at 22 months of age, she had short stature (1 cm below the 3rd centile), her anterior fontanelle was wide open, and she showed the same facial phenotype with hypertelorism as her brother (fig 6). She had small, translucent teeth.

X-ray examination of the skull showed multiple Wormian bones. There were no radiographical abnormalities of her legs. The mother of the children also had small, somewhat translucent, and brownish teeth. On x-ray examination of her skull, hands, and legs, no abnormalities were seen.

Discussion

We report on a 6 year old boy with Wormian bones, dentinogenesis imperfecta, and bone fragility owing to peculiar cortical defects which were first recognised at the age of 4½ years. His 22 months old sister presented with an identical picture, apart from the cortical lesions. Whether the distinct bilateral wave-like cortical defects are age related is not known at present. Further radiographical follow up will answer this question.
The differential diagnosis of skeletal dysplasias with Wormian bones, multiple fractures, and dentine abnormalities involves the different types of osteogenesis imperfecta (OI) and some essentially private syndromes.

The features of both sibs show considerable overlap with the clinical presentation of OI. OI is a well known generalised connective tissue disorder which has been classified into four major groups (OI types I to IV). Because of biochemical and genetic heterogeneity, OI shows wide variability of phenotypic presentation from early lethality to a mildly increased incidence of fractures. All forms of OI are the result of defects in the formation of type I collagen resulting from mutations in the COL1A1 gene on chromosome 17 and the COL1A2 gene on chromosome 7, which encode the production of two pro α1 chains and one pro α2 chain, respectively. Most cases of mild OI are the result of different mutations in these genes leading to a premature stop and a functional null allele, whereas most cases of severe OI are caused by mutations in the coding region of both genes resulting in the formation of an abnormal collagen. In a small subgroup of patients with the different types of OI, linkage studies exclude COL1A1 and COL1A2 as the causal sites. The cardinal feature of OI is osteopenia with, accordingly, an increased incidence of bone fractures, skeletal deformity, in particular bowing of the long bones, and short stature. Additional features are blue sclerae, deafness, ligamentous laxity, and dentino-ogenesis imperfecta in OI type IB, IIIb, and IVB. The patients presented in this report showed bone fragility, Wormian bones, dentine abnormalities, and mild short stature in common with patients with OI. However, the fractures in the index patient occurred because of unique cortical defects which are not known in OI and neither patient 1 or 2 had signs of osteopenia. Therefore, we do not believe this disorder to be a variant of OI, but a separate entity. This is corroborated but not proven by the normal results of collagen studies.

Hajdu-Cheney syndrome (acro-osteolysis, MIM *102500) has been considered as another differential diagnostic possibility. This disorder is characterised by cranial changes (Wormian bones and a thick calvarium with persistent sutures), predominantly phalangeal osteolysis, other skeletal abnormalities such as bowed ulna/ fibula, mesomelia and platypodyndyly, joint laxity, a distinct facial phenotype, and possibly cystic kidneys. Serpentine fibula syndrome (MIM 600330) is a disorder very similar to the former with, in particular, elongated and curved fibulae and polycystic kidneys. Both diagnoses were rejected in our patients because of the lack of osteolysis, the normal aspect of the spine, the lack of bowing of the long bones, and their facial phenotype being clearly different from Hajdu-Cheney and serpentine fibula syndromes.

We found only one published case report with similar findings, that of Suarez and Stickler in 1974. They reported on an 8 year old girl with identical cortical lesions of the tibiae and the long bones of the upper limbs, an increased incidence of fractures, epiphysial streaking, Wormian bones, short fifth fingers bilaterally, short fourth and fifth toes bilaterally, and short and thick arms. Her teeth were not described.

We suggest that patients 1 and 2 as well as the patient described by Suarez and Stickler suffer from the same type of skeletal dysplasia which is different from OI and from other syndromes with a combination of multiple fractures and Wormian bones. The characteristic radiological features seem to be pathognomonic and allow the differentiation from other disorders. Owing to the small number of patients, hypotheses on the mode of inheritance are limited to general reflections. One possibility is that the dentine abnormalities arose independently from the skeletal dysplasia in the family described here. In this case, the mother and children would have autosomal dominant opalescent dentine (dentinogenesis imperfecta type II, MIM *125490) and patient 1 and 2 concomitantly a new type of skeletal dysplasia. In this case, the inheritance of the skeletal disorder might be autosomal recessive, but, of course, a dominant disorder owing to gonadal mosaicism in one of the parents or a dominant disorder with incomplete penetrance cannot be excluded. Faced with two sibs with identical cortical lesions of the tibiae and one pro α1 and one pro α2 chain, respectively.

7 De Paepe A, Nuytinc L, Raes M, Frips JP. Homozygosity by descent for a COL1A2 mutation in two sibs with severe osteogenesis imperfecta and mild clinical expression in the heterozygotes. Hum Genet 1997;99:478-83.