The clinical features of homozygous $\alpha 2(I)$ collagen deficient osteogenesis imperfecta

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SUMMARY The detailed clinical features and progress of a child with homozygous $\alpha 2(I)$ collagen deficiency are described. Clinically, the disease presents as severe progressive Sillence type III osteogenesis imperfecta. The main biochemical defect is the synthesis of an abnormal pro $\alpha 2(I)$ chain which does not associate with pro $\alpha 1(I)$ chains and therefore is not incorporated into triple helical trimers of type I procollagen which can be used to assemble collagen fibres.

Osteogenesis imperfecta is a clinically and genetically diverse disorder of connective tissue typified by unusually fragile, brittle, osteoporotic bones, but other connective tissues are also faulty. Bone collagen consists almost entirely of type I collagen which contains two genetically distinct α chains in a triple helical heteropolymer with the composition $\alpha 1(I)_2\alpha 2$. The genes for $\alpha 1(I)$ and $\alpha 2(I)$ are located on chromosomes 17 and 7 respectively.¹⁻³

The best clinical classification of osteogenesis imperfecta has been formulated by Sillence *et al*⁴ who recognise four main types. Molecular abnormalities include over-hydroxylation of certain lysine residues⁵ and defects in the structure of $\alpha 1(I)$ or $\alpha 2(I)$ chains of type I procollagen.⁶⁻¹⁰ The structural alterations include deletions^{6,9} and point mutations within the collagen helix, in which arginine or glycine are mutated into cysteine. Here we detail the clinical features of a child with moderately severe early onset disease. The interesting observation in this patient was that his fibroblasts synthesised and secreted a pro $\alpha 1(I)$ trimer. The molecular defect is a mutation in the carboxyl propeptide of the pro $\alpha 2(I)$ chains which prevents their incorporation into triple helical procollagen molecules.

Case report

CLINICAL HISTORY

The proband was born in the 36th week of an

uncomplicated first pregnancy weighing 3 kg. Obvious abnormalities noted at birth included a small mandible, lumbar kyphosis, and a widely patent anterior fontanelle. At 5 weeks of age the humerus spontaneously fractured followed by a second break 2 weeks later. Although child battering was a possibility, he continued to fracture other bones spontaneously while an inpatient at the University of Gottingen Paediatric Department. Physical examination on hospital admission showed a large anterior fontanelle, a high arched palate, and large inguinal canals. Radiological studies showed multiple fractures. The changes included hypertrophic callus, relatively normal bony proportions, fractured ribs, and generalised osteoporosis. The skull was markedly osteoporotic with widened sutures and scanty wormian bones. The nature of the radiological changes were such as to exclude confidently both mild type I osteogenesis imperfecta and severe broad boned lethal type II osteogenesis imperfecta congenita (fig 1a-c).

PROGRESS

The infant was initially admitted to hospital for 5 weeks but conventional splinting of the broken limbs was followed by new fractures. Subsequently he was treated at home and, although fracturing as often as ten times monthly, he was sufficiently symptom free to be splinted at home by his mother after telephone counselling. Although the body length remained normal, by the age of 21 months his limbs were disproportionately shortened. His face showed the characteristic sunset sign induced by the

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FIG 1 X-ray appearances aged 5 months. The calvarium (a) is poorly calcified and upper and lower limbs show old and recent fractures with tibial, femoral, humeral, and radioulnar bowing (b,c). The appearances are not those of broad boned lethal nor of mild type I osteogenesis imperfecta.

unusual prominent and overhanging forehead (fig 2). The teeth were clinically normal and had erupted at the proper time and in the correct sequence. Mental development and IQ had been unusually advanced from the first and because of the extra attention given by his devoted mother he was unusually articulate and alert. Motor development was retarded as he had never been encouraged by his parents to walk or crawl and instead was transported either on a board or a specially modified baby chair.

PRESENT STATUS

In May 1983 the 5 year old child was re-examined and showed the following clinical features. He was small for his age and was at the 10th centile for body length but immeasurable in height because of his severely deformed limbs (fig 3a). The upper arms were abnormally short and the right contained a mid-humeral pseudoarthrosis which allowed independent rotation of 270° (fig 4a). The lower limbs were severely twisted and proximally shortened and had a frog-like appearance at rest. The severe tibial bowing noted previously at the age of 21 months had worsened. The face was relatively normal and had improved from before (fig 3b, c). The lateral appearance showed occipital flattening probably caused by persistently lying in the prone

FIG 2 Clinical appearance of affected child aged 21 months. Note overhanging forehead producing the so-called 'sunset sign' in which the eyes are both deviated inferiorly. The sclerae are blue and the teeth normal. All four limbs are splinted because of recent fractures and there is already significant tibial bowing.

FIG 3 Clinical appearance of the child aged 5 years. The general view shows the relatively normal body but emphasises the severe limb deformities and frog-like posture (a). The face is now relatively normal and the forehead much less prominent than in fig 2. The skull is moulded anteroposteriorly possibly from continuously lying prone (c). The teeth remain clinically normal. All the upper limb bones are severely preshortened. The lower parts of the legs have very severe bowing although the hands and feet have a normal appearance and proportions.

FIG 4 Arms and hands of proband showing (a) unusual hypermobility of right upper arm because of a humeral pseudoarthrosis and (b) normally proportioned hands and hypermobile fingers.

position. The joints were lax and hypermobile (fig 4b) and the skin was of soft and silky texture with a prominent venous network. The hands and feet had normal proportions (fig 3a) and the teeth were clinically normal (fig 2).

RADIOLOGICAL APPEARANCES

Both upper and lower limbs were unusually thin and markedly deformed. Particular abnormalities in-

cluded popcorn deformities of the knees (lower femur and upper tibiae) (fig 5d), the grossly deformed and fractured tibiae, and the right humeral pseudoarthrosis (fig 5a, b). There was obvious generalised osteoporosis with generalised vertebral collapse (fig 5c). The hands were relatively normal and the skull showed anteroposterior compression, wormian bones, and relatively normal teeth without dentinogenesis (fig 5e).

FIG 5 X-ray appearances of child aged 5 years. There is considerable deterioration in comparison with fig 1. This is typified by the appearances of the limbs which now show gross osteoporosis, extreme fragility, and multiple fractures (a, b, d). Notable features include the right humeral pseudoarthrosis (b) and the popcorn expansion of the knee joint (d). There is gross codfish deformity of the lumbar spine from osteoporosis and vertebral collapse (c). The lateral skull shows a few wormian bones and anteroposterior shortening (e). Notably the teeth are normal and the normal pulp cavities exclude dentinogenesis imperfecta.

ROUTINE BIOCHEMICAL INVESTIGATIONS

Except for an inappropriately high alkaline phosphatase (880 to 1440 IU/l), all conventional biochemical studies were normal except for medications. A variety of systemic medicaments including calcium, vitamin D, magnesium chloride, sodium fluoride, vitamin C, and fluoride derivatives were uniformly ineffective.

SPECIAL INVESTIGATIONS

We have described the specific biochemical abnormalities causing this disease elsewhere.^{11 12} In brief, this patient secretes a procollagen which does not contain $\alpha 2(I)$ chains. Procollagen $\alpha 2(I)$ chains transiently appear within cultured skin fibroblasts in diminished quantities (fig 6) but are not incorporated into the collagen triple helix.^{13 14} Nuclease S1 mapping and Southern blotting has located an 18 base pair deletion in the carboxylpropeptide of the pro $\alpha 2(I)$ chain.¹⁵ The patient is a homozygote for this defect and his consanguineous parents are both heterozygotes.

Apparently, $\alpha 2(I)$ is not essential for fibril assembly

FIG 7 Transversely sectioned collagen fibrils from skin of affected patient. The size and shape of the fibrils were normal except for focal areas of disorganisation in which the fibrils were misshapen and disturbed. Mean diameter 81.5 ± 17.8 nm, range 47.6 to 119 nm. Horizontal bar—100 nm. Original magnification $\times 84\,000$

FIG 6 Densitometric tracings of intracellular procollagens produced in culture and electrophoresed in 4% polyacrylamide. (a) control fibroblasts, (b) osteogenesis imperfecta fibroblasts.

since, even in its absence, collagen fibril banding appears to be normal. In transverse sections the fibrils are mostly normal except for focal areas of disorganisation in size and shape (fig 7).

Comment

This observation of a collagen totally deficient in $\alpha 2(I)$ chains is unique and is the first proven example of a homozygous protein abnormality in Sillence type III osteogenesis imperfecta.

References

- Huerre C, Junien C, Weil D, *et al.* Human type I procollagen genes are located on different chromosomes. *Proc Natl Acad Sci USA* 1982;**79**:6627–30.
- Junien C, Weil D, Myers JC, *et al.* Assignment of the human pro $\alpha 2(I)$ collagen structural gene (COL1A2) to chromosome 7 by molecular hybridization. *Am J Hum Genet* 1982;**34**:381–7.
- Sykes B, Solomon E. Assignment of a type I collagen structural gene to chromosome 7. *Nature* 1978;**272**:548–9.
- Sillence DO, Senn A, Danks DM. Genetic heterogeneity in osteogenesis imperfecta. *J Med Genet* 1979;**16**:101–16.
- Trelstad RL, Rubin D, Gross J. Osteogenesis imperfecta congenita. Evidence for a generalized molecular disorder of collagen. *Lab Invest* 1979;**36**:501–8.
- Byers PH, Barsh GS, Peterson KE, *et al.* Molecular mechanisms of abnormal bone matrix formation in osteogenesis imperfecta. In: Veis A, ed. *The chemistry and biology of mineralized connective tissues*. New York: Elsevier/North Holland, 1981:213–22.
- Barsh GS, David KE, Byers PH. Type I osteogenesis imperfecta, a nonfunctional allele for pro $\alpha 1(I)$ chains of type I procollagen. *Proc Natl Acad Sci USA* 1982;**79**:3838–42.

- ⁸ Barsh GS, Byers PH. Abnormal secretion of type I procollagen in a variety of osteogenesis imperfecta. *Proc Natl Acad Sci USA* 1981;**78**:5142-6.
- ⁹ Chu ML, Williams CJ, Gugliemina P, *et al*. Internal deletion in a collagen gene in a perinatal lethal form of osteogenesis imperfecta. *Nature* 1983;**304**:78-80.
- ¹⁰ Peltonen L, Palotie A, Hayashi T, *et al*. Thermal stability of type I and type III procollagens from normal human fibroblasts and from a patient with osteogenesis imperfecta. *Proc Natl Acad Sci USA* 1980;**77**:162-6.
- ¹¹ Nicholls AC, Pope FM, Schloon H. Biochemical heterogeneity of osteogenesis imperfecta: new variant. *Lancet* 1979;**i**:1193.
- ¹² Pope FM, Nicholls AC. Clinical, genetic and biochemical heterogeneity of osteogenesis imperfecta. In: Veis A, ed. *The chemistry and biology of mineralised connective tissues*. New York: Elsevier/North Holland, 1981:223-7.
- ¹³ Deak S, Chu ML, Nicholls AC, *et al*. A form of osteogenesis imperfecta in which the mRNA for pro $\alpha 2(I)$ is inefficiently translated in fibroblasts. *Fed Proc* 1982;**42**:852.
- ¹⁴ Deak S, Nicholls AC, Pope FM, *et al*. The molecular defect in a non-lethal variant of osteogenesis imperfecta: synthesis of pro $\alpha 2(I)$ chains which are not incorporated into trimers of type I procollagens. *J Biol Chem* 1983;**258**:5192-7.
- ¹⁵ Dickson LA, Pihlajaniemi T, Deak S, *et al*. Nuclease S1 mapping of a homozygous mutation in the carboxy-propeptide coding region of the pro $\alpha 2(I)$ collagen gene in a patient with osteogenesis imperfecta. *Proc Natl Acad Sci USA* (in press).

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