OSTEOGENESIS IMPERFECTA WITH DOMINANT INHERITANCE
AND NORMAL SCLERAE

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Most patients with dominantly inherited osteogenesis imperfecta have blue sclerae and relatively mild symptoms. However, in a small group of families the patients have normal sclerae and this disorder has been classified as Type 4 osteogenesis imperfecta. This paper reports the clinical and radiographical features of 48 patients from 16 families with Type 4 osteogenesis imperfecta and compares the findings with those of the classical disorder with blue sclerae (Type 1 osteogenesis imperfecta). The two types are similar in usually causing a mild disease but with a wide range of severity, and in both types the rate of fracture declines in adolescence. There are, however, some significant differences apart from the colour of the sclerae. In Type 4 the first fracture more commonly occurs at birth, dentinogenesis imperfecta is more frequent than in Type 1 and bruising and nose-bleeds are less common. As in Type 1, the radiographic appearances of the bones may be normal. It is important that Type 4 osteogenesis imperfecta should be recognised because of the need for competent genetic counselling, because the management may be different from that appropriate for Type 1 and because it may be mistaken for idiopathic juvenile osteoporosis or child abuse.

It has become increasingly clear that osteogenesis imperfecta is not a single disorder but a group of diseases, probably all resulting from defects in the molecular structure of collagen. Silence, Senn and Danks (1979), on the basis of their experience of 155 patients in Victoria, Australia, suggested that there are four distinct varieties of osteogenesis imperfecta: Types 2 and 3 are severe and probably inherited in an autosomal recessive manner and Types 1 and 4 are usually milder and inherited in an autosomal dominant manner. Their Type 1 is the classical osteogenesis imperfecta tarda in which the first fracture occurs typically in the second or third year of life; the sclerae are blue and deafernless is a common complication in adult life. Type 1 patients comprised the largest group (115 cases) in their survey. They also described two families (eight patients) with a mild disease of autosomal dominant inheritance but whose sclerae were normal. They felt that this disorder represented a distinct variant of osteogenesis imperfecta and called it Type 4. Some large series of patients with osteogenesis imperfecta included no cases of this type (Smith, Francis and Bauze 1975; Wynne-Davies and Gormley 1981) but Silence and his colleagues were able to find published reports of four other families who may have had the same disorder. They felt that this syndrome was more common than the few reports in the literature suggested. This paper reports the clinical and radiographical features of the disorder and compares the findings with those in patients with dominant osteogenesis imperfecta with blue sclerae.

CLINICAL MATERIAL AND METHODS

This work was part of a large survey of osteogenesis imperfecta in the British Isles. Forty-eight patients from 16 families with Type 4 osteogenesis imperfecta were studied; all the patients were from families in which at least two members were affected in different generations. Although patients who probably represented new mutations of Type 4 osteogenesis imperfecta were seen, they have not been included in the present study. For comparison 69 patients from 30 families with classical osteogenesis imperfecta tarda (Type 1) were also studied.

Patients, or their parents, completed a questionnaire designed to facilitate processing by computer. Thirty-six of the 48 patients with Type 4 osteogenesis imperfecta and 58 of the 69 patients with Type 1 osteogenesis imperfecta were seen personally by CRP; particular note was made of the patient's height, the shape of the skull, the colour of the sclerae and evidence of dentinogenesis imperfecta. Radiographs were also reviewed in 11 of the Type 4 patients and 17 of the Type 1 patients.

RESULTS

Type 4 osteogenesis imperfecta is considerably less common than Type 1. At the time when the data used in this paper were being collected we had full details of 16 families with Type 4 compared with 71 families with Type 1. A comparison of the classical features found in the two types of osteogenesis imperfecta is summarised in Table I.
Table 1. Some clinical features of osteogenesis imperfecta: comparison of Types 1 and 4

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Percentage of patients</th>
<th>Significance (P)</th>
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<tbody>
<tr>
<td>Fractures at birth</td>
<td>Type 1: 12.3</td>
<td>Type 4: 28.3</td>
</tr>
<tr>
<td>Deafness in patients aged over 30</td>
<td>Type 1: 50.0</td>
<td>Type 4: 29.4</td>
</tr>
<tr>
<td>Dentinogenesis imperfecta</td>
<td>Type 1: 40.6</td>
<td>Type 4: 68.8</td>
</tr>
<tr>
<td>Bruising</td>
<td>Type 1: 78.3</td>
<td>Type 4: 36.4</td>
</tr>
<tr>
<td>Nose-bleeds</td>
<td>Type 1: 29.0</td>
<td>Type 4: 9.1</td>
</tr>
<tr>
<td>Double-jointedness</td>
<td>Type 1: 44.9</td>
<td>Type 4: 43.8</td>
</tr>
<tr>
<td>Dislocations</td>
<td>Type 1: 29.0</td>
<td>Type 4: 25.0</td>
</tr>
<tr>
<td>Herniae</td>
<td>Type 1: 7.2</td>
<td>Type 4: 6.8</td>
</tr>
<tr>
<td>Fractures of the skull</td>
<td>Type 1: 13.0</td>
<td>Type 4: 19.1</td>
</tr>
<tr>
<td>Fractures of the ribs</td>
<td>Type 1: 20.3</td>
<td>Type 4: 31.9</td>
</tr>
<tr>
<td>Excessive sweating</td>
<td>Type 1: 44.1</td>
<td>Type 4: 56.3</td>
</tr>
<tr>
<td>Skull shape</td>
<td>tam-o'-shanter</td>
<td>Type 1: 10.5</td>
</tr>
<tr>
<td>inverted triangle</td>
<td>Type 1: 42.1</td>
<td>Type 4: 31.6</td>
</tr>
</tbody>
</table>

The significance of the differences between the two groups was calculated using the χ² test. NS = No significant difference (P > 0.05).

**Age at first fracture.** Figure 1 shows the age of each patient at the time of the first known fracture. While the spread is considerable, the proportion of patients with fractures first identified at the time of birth was notably higher in Type 4 than Type 1 osteogenesis imperfecta.

**Total number of fractures.** There is a very wide variation in the severity of the disease as judged by the number of fractures in both Type 4 and in Type 1 (Fig. 2). Two individuals in each group had no recorded fractures although they were undoubtedly affected on the basis of family history and other signs. In both groups the rate of fracture was maximal during the first 15 years of life and fell after puberty and during adult life (Fig. 3). The number of older patients is as yet too small to say whether the rate of fracture increases after the menopause.

**Colour of sclerae.** All the patients with Type 1 osteogenesis imperfecta had blue or grey sclerae which remained abnormal throughout life. Many parents of affected children asserted that the colour of the sclerae varied from time to time, becoming darker when fractures occurred. By contrast, the sclerae of almost all the patients with Type 4 osteogenesis imperfecta were normal although seven of the youngest patients had pale blue sclerae, and the parents of 12 of the others thought that the sclerae had been pale blue in early childhood. In none of the adolescents or adults with Type 4 osteogenesis imperfecta were the sclerae abnormal.

**Teeth.** In both groups dentinogenesis imperfecta was either consistently present or consistently absent within each family for the patients seen personally. While in many cases the deciduous teeth were more severely affected than the permanent teeth, it was not difficult to detect the fragile, discoloured teeth, particularly in the lower jaw, in patients of all ages. However, dentinogenesis imperfecta was significantly more common in Type 4 than in Type 1. In some families with Type 4 osteogenesis imperfecta the dental abnormalities were the one con-
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explained the selves 4. considerably osteogenesis One Type VOL. I. JANUARY 1983

Fractures per person per year in the two groups of patients.

sistent marker when the other clinical features varied greatly from person to person.

Other clinical features. A tendency to bruising and nose-bleeds was significantly less common in Type 4 than in Type 1. Fractures healed at a normal rate in both types. Table 1 shows the incidence of excessive sweating, of abnormalities of the skull, of double-jointedness and the history of herniae in both groups.

Variation in clinical manifestations. As in Type 1 osteogenesis imperfecta, the severity of the disease varied considerably within most of the large families with Type 4. Frequently parents of affected children were themselves affected but did not appreciate the fact because of the minor nature of their symptoms and the lack of fractures. Such affected individuals often regarded the few fractures they had sustained as being adequately explained by the trauma involved. Figure 4 shows the pedigree of one such family in which initially the propositus was regarded as a sporadic case of osteogenesis imperfecta. Her mother (Case 2) became deaf at the age

of 32 and had had a fractured skull. Her grandmother (Case 3) became deaf at the age of 23 and had had three fractures of the forearm which were thought to have been adequately explained by the trauma; in later life she had a tam-o'-shanter skull. A great-grandmother (Case 4) and an aunt (Case 5) were both deaf at an early age and were thought to have had skulls of abnormal shapes; neither had sustained fractures. A great-aunt (Case 6) was deaf from the age of 14 and had sustained three fractures which were thought to have been adequately explained. Her daughter (Case 7) had had no fractures and no deafness. A granddaughter (Case 8, a second cousin of the propositus) had sustained bilateral femoral fractures soon after birth when being tested for congenital dislocation of the hips and was also found to have several fractured ribs. It is of interest that the four affected members of this family seen by CRP (Cases 1, 2, 3 and 5) had denticogenesis imperfecta, and that all the remaining affected people were reported by relatives to have had abnormal teeth.

Radiography. Radiographs were obtained for 17 of the patients with Type 1 osteogenesis imperfecta and 11 of the patients with Type 4 osteogenesis imperfecta. In both groups radiographs taken at the time of the first fracture were usually normal in other respects, with no suggestion of osteoporosis or of other abnormalities of the texture of the bone. Osteoporotic deformities and cystic changes were common later in childhood and in adulthood in bones which had sustained frequent fractures. It seems likely that many of the reported radiographic abnormalities are the result of the fractures and of their treatment, rather than manifestations of the underlying disease. This is illustrated in Figure 5 which shows the legs of one patient (Case 1 in Figure 4). She had never had a fracture
of the tibiae or fibulae, but the right tibia and fibula are grossly abnormal compared with those on the left, presumably because the right leg had been immobilised on many occasions during the treatment of fractures of the femur. This figure also shows the bowing which was noted frequently among patients with Type 4 osteogenesis imperfecta. More detailed studies of radiographs from larger numbers of patients are in progress.

**DISCUSSION**

It is important to appreciate that blue sclerae are not always a feature of patients with mild or moderately severe, dominantly inherited osteogenesis imperfecta. Patients with normal sclerae differ from those with blue sclerae in several respects and we agree with Silence and his colleagues (1979) that Type 4 should be regarded as a distinct variant. We feel that it is important that this disorder should be clearly recognised, first to ensure competent genetic counselling, secondly to determine the surgical management which may differ from that appropriate for Type 1 and thirdly to distinguish it from idiopathic juvenile osteoporosis and from non-accidental injury. In addition accurate identification of the different clinical varieties of osteogenesis imperfecta is an important prerequisite for studying the underlying abnormalities of collagen (Müller et al. 1977; Nicholls, Pope and Schloot 1979; Peltonen, Palotie and Prockop 1980; Francis et al. 1981).

**Genetic counselling.** Genetic counselling may be difficult in some families with Type 1 osteogenesis imperfecta in that the disorder is variable in expression, and some affected individuals have no fractures but only the blue sclerae. The problems are considerably greater in Type 4 osteogenesis imperfecta because of the lack of blue sclerae as a marker of the disease and also because of the extreme variability of expression. In some cases, however, as in the family we have described, the presence of dentinogenesis imperfecta can provide a valuable marker. In an apparent sporadic case of Type 4 osteogenesis imperfecta it is important to study carefully the parents and other members of the family to determine whether there are any features to suggest osteogenesis imperfecta, notably abnormalities of the shape of the skull, premature deafness, dentinogenesis imperfecta and abnormal metacarpals (Paterson 1978), as well as fractures. In the absence of any such features it is likely that the disorder is due to a new mutation and further children of the same parents are unlikely to be affected.

**Operative management.** This study suggested that there may be differences in the way in which the bones behave between Type 1 and Type 4 osteogenesis imperfecta. It was a clinical impression that bending of a bone, resulting in the extrusion of an intramedullary pin, was more common in Type 4 than in Type 1. If this finding is confirmed in larger series it may be that other forms of fixation would be more appropriate in Type 4 osteogenesis imperfecta.

**Differential diagnosis.** The differential diagnosis of Type 4 osteogenesis imperfecta from idiopathic juvenile osteoporosis and from non-accidental injury can be very difficult since the sclerae are seldom abnormal even in early childhood and since there may be no clear family history of the disorder. Children whose first fracture is in early childhood are more likely to have Type 4 osteogenesis imperfecta than idiopathic juvenile osteoporosis but in later childhood the differential diagnosis is more difficult. However if, at the time of the first fracture, radiographs appear to be normal in other respects then Type 4 osteogenesis imperfecta is likely. It is not surprising that fractures for which the parents can give no adequate explanation may readily be confused with non-accidental injury in children with osteogenesis imperfecta and normal sclerae. In the present series, limited to patients with a family history, this was a problem only in one child who was taken into the care of the local authority on two occasions before the diagnosis became clear. Cases of Type 4 osteogenesis imperfecta arising as a new mutation can be very difficult to diagnose and it is important to search for all the features of the disorder, to make a detailed study of the family history and also to seek out features of non-accidental injury other than fractures and bruising. No biochemical tests of plasma or urine or histological tests on skin or bone are currently known to be helpful.

**Heterogeneity.** Recent studies have indicated that Type 1 osteogenesis imperfecta may be divided into two subtypes depending on the presence or absence of dentinogenesis imperfecta (Levin, Brady and Melnick 1980). It seems likely that a similar subdivision may be applicable in Type 4 when a larger number of cases is available for study.

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**REFERENCES**


