Osteogenesis imperfecta type IIA: evidence for dominant inheritance

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SUMMARY Thirty cases of radiologically proven type IIA osteogenesis imperfecta (OI) have been ascertained. All were isolated with 19 unaffected foreborn and 19 unaffected afterborn sibs. Two sets of parents, both Asian, were consanguineous. There was a significant parental age effect, most marked for paternal age. It is concluded that most cases of type IIA OI result from new dominant mutations.

The year 1979 was to prove a watershed in the history of osteogenesis imperfecta (OI) with the publication by Sillence et al1 of a comprehensive classification embracing clinical, genetic, and radiological parameters. These authors identified “at least four distinct syndromes” falling within the spectrum of OI. Type I constituted the largest group of patients with autosomal dominant inheritance of osteoporosis, blue sclerae, deafness, and dentinogenesis imperfecta. Type II patients died in the perinatal period with crumpled femora and beaded ribs. Type III was characterised by severe, progressive deformity, while in type IV, patients showed dominant inheritance of osteoporosis leading to fractures but the normal sclerae.

In their original study, Sillence et al1 concluded that “some if not all” cases of type II OI, the perinatally lethal form, showed autosomal recessive inheritance. More recently type II OI has been subdivided into three forms, designated A, B, and C on the basis of radiological findings.2 Segregation analysis suggested that all three of these subgroups showed autosomal recessive inheritance.

However, other studies have noted a deficiency of affected sibs of probands with lethal OI,3 4 and a postal survey conducted in 1979 to 1980 seemed to confirm the prevailing anecdotal impression that, in the United Kingdom at least, affected sib pairs with lethal OI were extremely uncommon.5 This paper reports evidence from two studies carried out in parallel, which indicates that in type IIA OI, which constitutes the most common form of perinatally lethal OI, inheritance is more likely to be autosomal dominant than autosomal recessive in the majority of cases.

Type IIA osteogenesis imperfecta

The clinical and radiological features of type IIA OI were delineated by Sillence et al5 in 1984. The babies usually die before or shortly after birth with median survival of two hours. Clinically these infants have a small chest and short, bowed limbs, with the thighs held in abduction (fig 1). They also have a rounded face, short neck, and relatively large head which on palpation reveals a very soft membranous skull.

Radiologically there is almost complete lack of mineralisation in the skull, with at most a thin rim of calvarial calcification, thick continuously beaded ribs particularly evident in ribs 7 to 10, platspondyly usually involving more than half of the thoracic and lumbar vertebral bodies, short, broad femora with little or no modelling, and sharply angulated tibiae (fig 2). These features differ from those of type IIB OI in which the ribs are thinner with discontinuous beading, and from type IIC OI in which thin, discontinuously beaded ribs are associated with poor modelling of the long bones.

Patients and ascertainment

Cases were ascertained through the records of the Clinical Genetics Units throughout Great Britain; these were invited to participate by providing details of families referred with a history of perinatally lethal OI. When possible home visits were carried out to these families to construct pedigrees and examine close relatives. When this was not possible,
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Details were obtained directly from the records of the referral centres and attempts were made to update the pedigree by correspondence with the family's General Practitioner. One case was ascertained through the Brittle Bone Society during the study described in the following paper.

Results

In reviewing the radiology of the 60 perinatally lethal cases for which x rays were available, a clear group emerged comprising the majority of the patients, in which the radiological features were typical of type IIA OI. This group consisted of 27 cases plus three cases in which the radiological findings were generally consistent with type IIA but the ribs, while showing almost continuous beading, were thinner than normal in type IIA, but thicker than in types IIB and IIC. A further two cases also showing radiological features overlapping between types IIA and IIB were classified as probable type IIB and are excluded from this analysis.

Thus the study group consisted of 30 cases, of which 21 were liveborn, five stillborn, and four were terminated after routine second trimester ultrasound. There were 16 males, 12 females, and two babies, both terminations, of unknown sex. For the liveborn infants the mean period of gestation was 36-4 weeks and median and mean periods of survival were 30 minutes and four hours respectively. Details of mode of delivery were obtained for 18 babies, eight of whom were delivered by caesarean section, eight by breech extraction, and only two by normal vertex delivery. All of the liveborn babies were well below the 10th centile for length at birth. Necropsy reports were obtained for 18 babies, one of whom had additional malformations consisting of an atrial septal defect and bilateral ureteric stenosis. All of the 30 cases were isolated with no family history of OI. Twenty-five were born to unrelated Caucasian parents. The remaining five cases were delivered to parents originating from the Indian subcontinent: two of these couples were definitely consanguineous and in one couple remote consanguinity was suspected. The 30 cases had 19 foreborn and 19 afterborn sibs, all of whom were healthy with the exception of one of the foreborn sibs who had Kugelberg-Welander disease: it was the parents of this child who were believed to be distant cousins. A total of 13 miscarriages had occurred in the 30
sibships, with one mother having experienced five first trimester losses.

Mean parental ages at birth are given in the table. There was a significant paternal and maternal age effect, more so for paternal age, when compared with the general population values for England and Wales in 1982,6 the modal year of birth of the study cases. Fourteen fathers and six mothers were aged over 35 years at the time of birth of their affected child.

Discussion

Existing biochemical and genetic data indicate that OI is likely to result from single gene defects involving collagen genes. Thus sporadic cases could result from autosomal recessive inheritance or represent new dominant mutations. The evidence presented in this paper strongly favours the latter as the probable explanation for the origin of most cases of type IIA OI. No affected sib pairs were ascertained, even though clinical genetics centres would be particularly likely to know of affected sib pairs, and no consanguinity was observed among the Caucasian parents. Consanguinity was noted among the Asian parents, but consanguinity is common in certain Asian populations and consequently of doubtful significance. Additional support for the majority being new dominant mutations comes from the increased paternal age effect.

To try to ensure as far as possible that affected sib pairs are indeed uncommon in Great Britain, the authors wrote to all members of the British Association for Perinatal Paediatrics asking if members knew of any families in which there had been more than one child with lethal OI. No positive responses for definite type IIA OI were received.

Support for the concept that type IIA OI may result from new dominant mutations comes from recent biochemical and molecular studies. The case originally reported by Heller et al.7 and Pentinnen et al.,5 in which reduced collagen synthesis was noted, probably had type IIA OI, albeit a particularly severe form since decapitation occurred at delivery.

Fibroblasts cultured from this infant were found to synthesise two distinct pro α1(I) chains, one normal and one abnormal.9 Subsequently a deletion of approximately 0.5 kb was shown in one pro α1(I) allele.10

If the abnormal gene product is synthesised and incorporated into the type I procollagen molecule, thus preventing normal folding into a triple helix, then since each trimer contains two pro α1(I) chains on average three out of every four molecules will contain at least one abnormal chain resulting in degradation, a concept described as ‘protein suicide’.11 Perhaps more apt are the terms ‘included mutants’ and ‘excluded mutants’ coined by Sykes.12 Included mutants will be more deleterious than mutant chains which are so abnormal that synthesis or secretion or both are prevented, that is, excluded mutants. The mechanism explains how a new dominant mutation in one α1(I) gene could result in severe phenotypic effects. Results published recently indicate that collagens synthesised by fibroblasts from several patients with unspecified forms of type II OI were consistent with heterozygosity for an abnormal allele of one of the type I collagen genes, that is, new dominant mutations.13-15

These observations tend to conflict with the conclusions of Silence et al.1,2 that all forms of type II OI are likely to be autosomal recessive. In their studies the proband method of segregation analysis was used, a method appropriate for multiple incomplete ascertainment.16 If, instead, the sib method had been applied to the families with type IIA OI in table 1 of reference 2, a segregation ratio of 0.128 with a standard error of 0.05 would have been obtained. This table contained 28 sibships with type IIA OI, only three of which contained more than one affected child. Two of these three sibships had been published previously and were being reported.

Given the nature of the collagen molecule and its complex post-translational modification, it would not be too surprising if type IIA is indeed genetically heterogeneous. It is certainly possible that different mutations at the same locus could lead to either dominant or recessive inheritance. This study does not exclude a small proportion of type IIA cases being autosomal recessive and there are a few reports of sib pairs with definite type IIA.17 18 A strong case can be made for reassessing the radiology in any type II sib pairs to try to define the characteristic features of the recessive forms.

Prenatal diagnosis was achieved using routine obstetric ultrasonography for four of the cases in this study. The x ray of one of these babies is shown in fig 3, which shows that the characteristic radiological changes are present at an early stage in utero. Two

<table>
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<th>TABLE</th>
<th>Type IIA OI: parental ages at birth.</th>
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<tr>
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<td>Study cases</td>
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<td>Mean paternal age (y)</td>
<td>34.19±7.17 (n=28)</td>
</tr>
<tr>
<td>Mean maternal age (y)</td>
<td>28.87±6.23 (n=30)</td>
</tr>
</tbody>
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Farndon for permission to reproduce figs 2 and 3 respectively. IDY wishes to thank the Trent Regional Health Authority Research Committee for financial support. EMT was supported by a Wellcome Trust Training Fellowship.

References

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of the babies in this series were delivered by elective caesarean section so that it is unlikely that the severe skeletal abnormalities are the result of trauma sustained during labour.

Until the genetics of type II AOI are fully clarified, it would seem prudent to offer prenatal diagnosis to all mothers who have had an affected baby. Our experience indicates, however, that the likelihood of recurrence is very low.

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FIG 3 Radiograph of a fetus terminated at 20 weeks' gestation after detection by routine obstetric ultrasonography. The typical features of type II AOI are already apparent.
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