Asphyxiating thoracic dysplasia

Clinical, radiological, and pathological information on 10 patients

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SUMMARY Review of 10 cases of asphyxiating thoracic dysplasia has shown a wide range of clinical effects and some variability in the radiographic features. Respiratory difficulty was severe in 7 babies and lethal in 6 of these. The seventh child is remarkable for his normal stature and excellent health at 15 years of age. 3 babies had no respiratory difficulty but 2 of them subsequently died of renal failure; one remains alive at 3 years. Microscopical abnormalities in the liver and kidneys were very frequent and appeared to increase progressively with age.

The condition originally described by Jeune et al. (1955) as asphyxiating thoracic dystrophy (ATD) was subsequently delineated clearly by several reports, including that of Langer (1968) who suggested the title thoracic-pelvic-phalangeal dystrophy. This described the distribution of the diagnostic features well and avoided the implication that asphyxia is a constant feature or that all bone dysplasias which cause asphyxia are the same. Unfortunately the International Committee on the Nomenclature of Bone Dysplasias chose 'asphyxiating thoracic dysplasia (Jeune)' (Maroteaux et al., 1970) and the term has been misused. Many patients do die of respiratory failure in infancy and those who survive may develop progressive renal disease (Herdman and Langer, 1968). Hepatic changes have also been described in a few cases (Edelson et al., 1974).

We describe 10 patients seen in Melbourne in the past 12 years and attempt to provide some perspective regarding the pattern of the illness. The diagnostic radiological features are described and the problem of distinction from the Ellis-van Crevel syndrome is discussed.

Case ascertainment and incidence

Radiological and clinical records of all teaching and public hospitals in Victoria were searched for patients with bone dysplasias. Over 400 patients were identified in all, including 10 patients with ATD, 9 of whom were already known to us. 2 additional stillborn babies were excluded from the study because only radiographs were available and they did not allow distinction between ATD and the Ellis-van Crevel syndrome.

Ascertainment has been prospective and probably complete since 1965. 5 definite cases occurred (plus the 2 in whom the diagnosis is uncertain) in this period during which 650 000 children were born. The frequency of ATD is therefore estimated to be between 1 in 100 000 and 1 in 130 000 live births. Data regarding sibs are presented in the Table. No parental consanguinity or relevant illness was found in other relatives.

Investigations

Clinical features (Table). Respiratory distress was very severe in the neonatal period in 7 babies. 2 of these babies died on the first day and 4 more died 5 weeks to 3 years after constant or recurrent respiratory distress, combined with renal failure in the longest survivor. The seventh baby (Case 9) suffered respiratory symptoms sufficient to warrant prolonged hospital treatment in the first months of life, but then progressively 'grew out of his disease'. He is now a healthy 15-year-old of good physique and normal stature. However, his chest remains noticeably small (Fig. 1). His mother states that his younger brother and sister both followed a similar course without referral to hospital and they certainly share his mild thoracic deformity.

The remaining 3 patients presented because of dwarfism, short limbs, and/or chest deformity, but suffered no respiratory symptoms. 2 subsequently
developed renal failure at 2–3 years of age and died. The last child is alive and clinically well at 3 years. No renal biopsy has been performed.

Radiological features. All young babies had short ribs expanded and flared anteriorly. Rib shortening varied from extreme (Fig. 2) to moderate (Fig. 5). Rib growth improved remarkably after infancy, especially in Case 9.

Pelvic changes comprised shortening of the ilia with spiky protrusions at lateral and medial edges of the horizontal acetabulum, and anteriorly (giving a trident appearance). Similar spikes of ossification were seen at the margins of the narrow sacroiliac notch and at the metaphyses of the long bones. Severe changes are shown in Fig. 4a and mild changes in Fig. 4b and Fig. 5.

Phalangeal changes were minimal in the newborn period except in Case 6 whose changes were unusual in degree and quality (Fig. 3b). Cone-shaped epiphyses (Fig. 3a) developed later in all survivors except Case 9. Polydactyly was present in 3 patients.

Pathological features. Kidney sections were available from 8 patients, obtained at necropsy in 7 and by biopsy in 1. Abnormalities were found in all these 8 patients, but were minimal in Cases 4 and 5. The kidneys of the babies and younger children contained glomerular and tubular cysts, an increased amount of loose ‘embryonal’ connective tissue around some of the nephrons, and some abnormal tubules surrounded by concentrically arranged collagen fibres (Fig. 6). These abnormal structures were more numerous and obvious in the kidneys of the longest surviving patients than in those who died as infants.

In Cases 2 and 3, who died of renal failure, the changes of severe chronic pyelonephritis with scarring and distortion of the renal parenchyma largely obscured any dysplastic changes (Figs. 7 and 8). However, in some of the less damaged areas there were abnormal dilated tubules and small tubules lined by cuboidal cells with dense nuclei and surrounded by concentric layers of fibroblasts and collagen. In addition some small shrunken glomeruli were lined by cuboidal cells and the vessels were thick walled and tortuous.

Liver sections were examined at necropsy in 7
patients and all were abnormal. Portal tract fibrosis and proliferation of bile ducts were seen consistently (Fig. 9). Fibrosis was minimal in the youngest patients, but increased in proportion to age in those surviving beyond infancy. However the fibrosis remained confined to the portal regions and parenchymal changes were minimal. Bile duct proliferation was obvious and some ducts appeared to have no lumen. They occupied the peripheral part of the fibrotic portal tracts, often forming an incomplete ring around a central fibrotic portal zone.

The lungs of Cases 1, 2, 4, and 5 showed only changes due to infection. Hypoplasia and some dysplasia (groups of small alveoli separated by loose mesenchymal tissue) were present in Case 10. Bone histology was not studied in detail.

Case reports

Case 1. A male, suffered severe respiratory distress from birth, had short ribs and short limbs, required repeated admissions because of respiratory difficulty...
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Fig. 4 (a) Case 4. Typical infantile pelvic changes, aged 6 weeks. (b) Case 6. Mild pelvic changes, aged 13 months.

during chest infections, and finally died of respiratory failure at 16 months of age.

Case 2. A male, was noted to have a small chest and short stature from early infancy, but suffered no respiratory disability. ‘Achondroplasia’ was suggested at 19 months of age. Anaemia was noted at 2½ years and responded to iron therapy, but recurred at 3 years (Hb 5·1 g/dl) along with hypertension and uraemia (blood urea 500 mg/100 ml; 83 mmol/l). He was first seen at the Royal Children’s Hospital at this stage and skeletal x-rays showed ATD. He died of renal failure a few weeks later.

Case 3. A male, attended hospital in another state because of short stature and a small chest, but suffered no respiratory problems. He presented to the

Royal Children’s Hospital at 2 years with anaemia and dyspnoea due to renal failure. Blood pressure was 175/120, Hb 6·8 g/dl, and blood urea 312 mg/100 ml (51·8 mmol/l). He died of renal failure soon afterwards.
Case 4. A female, was noted to have respiratory distress and a very narrow chest at birth. She fed poorly, tired easily, and grew very slowly. Recurrent episodes of respiratory failure during mild respiratory infections finally ended in death at 3 months. She was the third child of unrelated parents. The first child was stillborn. The second child (female) died at 3 months of respiratory distress due to a very small chest. The fourth child is Case 5.

Case 5. A female, sister of Case 4, suffered respiratory distress from birth due to a very small chest. She died of respiratory failure at 4 weeks.

Case 6. A female, was admitted at 5 days because of jaundice and vomiting and was noticed to have a narrow chest and short limbs. Neonatal hepatitis was diagnosed on clinical and biochemical findings and she developed intestinal malabsorption and rickets. Proteinuria was noted but renal function was normal. Respiratory difficulty developed during each respiratory infection in infancy and she required artificial ventilatory support on one occasion. Raised blood urea was noted at 13 months and renal biopsy showed cystic dysplasia and fibrous changes. She died at 3½ years of renal and respiratory failure. Permission for necropsy was refused. Radiological findings were consistent with ATD though the pelvic changes were less marked than usual and the phalangeal changes were unusually severe (Fig. 3b). Osteoporosis was severe in the early stages, and was attributed to rickets. Metaphyseal irregularity increased with age, presumably as the result of renal failure.

Case 7. A male, was hypotonic and depressed at birth, developed severe respiratory distress, and died at 12 hours of age. He was noted to have a very narrow chest and short limbs.

Case 8. A female, was noted to have polydactyly and a small chest, but suffered no real respiratory difficulty. The liver and spleen were easily palpable. Microscopy and blood urea have remained normal. She is now 3 years of age and has a notably small chest, but is otherwise healthy.

Case 9. A male, was noted to have chest deformity and rapid respiration from birth. Dyspnoea and
feeding difficulty persisted for 6 months and he progressed poorly. Respiratory difficulties diminished subsequently and he thrived so well that when last seen at the age of 15 years he was a robust youth whose height was on the 25th centile. His only abnormality was a small chest (Fig. 5). Radiological appearances in infancy were those of ATD though the pelvic changes were less severe than usual (Fig. 5). At 15 years the ribs were still a little short but the pelvis was normal (Fig. 5). No phalangeal changes were apparent.

He had five sibs, 2 of whom were said to have suffered very similar respiratory difficulty in infancy. All 6 children were seen during childhood and it was quite clear that Case 9 and these 2 sibs had remarkably small rib cages when compared to the other 3 sibs. No radiographs were available for the apparently affected sister. The films of the affected brother were taken at the age of 3 years and the only abnormality was of the ilium.

Case 10. Born after a pregnancy complicated by hydramnios. The chest was very small and respiratory difficulty was severe from delivery. The baby died at 12 hours of age.

Discussion

The classical infantile manifestations of ATD comprise dwarfism with short ribs, short limbs, and characteristic radiographic changes in the ribs and pelvis (Langer, 1968; Jéquier et al., 1973). The x-ray findings are so typical that distinction from all bone dysplasias except the Ellis-van Creveld syndrome (Kozlowski et al., 1972) is possible. This final distinction can be made only by the presence of associated clinical features in the Ellis-van Creveld syndrome, i.e. polydactyly (which can occur in ATD), dysplasia or hypoplasia of the finger nails, natal teeth or dental cysts, abnormal frenula of the lips, and congenital heart defects. 2 stillborn babies were excluded from this study because no clinical information was available and x-rays did not allow distinction between these diseases. As patients grow
older the development of progressive renal failure may indicate that the condition is ATD.

The variation in severity of the clinical and radiological features in these 10 patients is worthy of comment. All had small chests clinically, but the degree of respiratory distress varied from negligible to rapidly lethal. The radiographic appearance of the ribs was consistent though the degree of rib shortening varied. The severity of the pelvic changes and of the prominence of the spiky protrusions on the metaphyses were particularly variable. It is this variation that leads to confusion in the use of the term ATD through inclusion of patients with short ribs, who lack the typical pelvic changes. The pelvic changes in Case 9 are considered sufficient to warrant inclusion.

Unfortunately some authors have used the term ATD as a general description for babies with bone dysplasias which cause a small chest. This tendency is most unfortunate and the term should be restricted to the specific entity described by Jeune (1955). The descriptive title of thoracic-pelvic-phalangeal dystrophy (Langer, 1968) seems preferable because the term ‘asphyxiating’ is not appropriate to all cases and leads to inappropriate use.

The improvement in the bone abnormalities with age was a very notable feature in those patients who lived more than a few months, and was quite remarkable in Case 9 who has only minimal residual changes in the rib cage at the age of 15 years. Case 6 also warrants special comment because of the extreme phalangeal changes along with mild pelvic abnormalities.

The renal and hepatic lesions also varied in degree with an overall trend towards increasing severity with increasing age. The hepatic changes comprised proliferation of small duct radicals in the portal tracts with portal fibrosis and were present in all 7 patients from whom tissue was available. Renal abnormalities were also present in all patients examined. 2 sibs (Cases 4 and 5) who died early had minimal renal lesions and renal tissue has not been examined microscopically in the 2 living patients. The boy who is healthy at 15 years (Case 9) seems very unlikely to have significant renal disease, but one cannot be so confident about the 3-year-old girl (Case 8).

The renal changes in individual cases of ATD have been described repeatedly, but hepatic changes have received less attention (Edelson et al., 1974). A few case reports describe patients who may have ATD with renal and hepatic lesions under different titles. Two very recent ones (Robins et al., 1976; Popović-Rolović et al., 1976) used the term nephronophthisis to describe the renal lesion, showed phalanges with coned epiphyses, and portal changes similar to those in this series. However, in the latter patient (Popović-Rolović et al., 1976) retinal pigmentary dystrophy and cerebellar ataxia were also present, as they were in the patient described by Mainzer et al. (1970). The radiological features of the patient of Robins et al. are compatible with a diagnosis of ATD (Chakera, 1975). The other reports contain too little radiographic information to comment further. There is clearly work to be done to determine the extent of the ATD syndrome and to separate it from other conditions with similar features.

The severity of respiratory distress in this condition leads to consideration of artificial ventilatory support and/or reconstructive surgery to the rib cage in some young babies. The high frequency of progressive renal failure casts some doubt upon the wisdom of such dramatic intervention. However, the existence of Case 9 indicates that survival with a normal life is possible for a few individuals. Some reliable method of early recognition of a progressive renal lesion is needed. Prospective study of each child with ATD by renal and liver biopsy may be warranted.

The distribution of the cases in the families in this study is compatible with autosomal recessive inheritance. Variability in severity between families and constancy within families is commonly encountered in recessively inherited diseases. Different allelic mutations may be present in each family.

References


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