Metaphyseal chondrodysplasia, neutropenia, and pancreatic insufficiency presenting with respiratory distress in the neonatal period

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Danks, D. M., Haslam, R., Mayne, V., Kaufmann, H. J., and Holtzapple, P. G. (1976). *Archives of Disease in Childhood*, 51, 697. **Metaphyseal chondrodysplasia, neutropenia, and pancreatic insufficiency presenting with respiratory distress in the neonatal period.** Two pairs of brothers suffered respiratory distress in the newborn period because their ribs were abnormally short. The diagnostic radiological features of metaphyseal chondrodysplasia appeared only in the second year. Pancreatic insufficiency and neutropenia were present. One died of overwhelming infection and his brother survived a life-threatening episode of gangrenous proctitis.

The syndrome of pancreatic insufficiency and neutropenia was described by Shwachman *et al.* (1964) and by Bodian, Sheldon, and Lightwood (1964). Burke *et al.* (1967) pointed out the association of metaphyseal chondrodysplasia with this syndrome in a patient from Melbourne. Giedion *et al.* (1968) and Shmerling *et al.* (1969) defined the syndrome more clearly and Sutcliffe and Stanley (1973) reviewed the bony features. Dwarfing has generally been moderate and has become apparent only after the first year or two of life. Rib shortening has not been a clinical problem. The neutropenia has varied in severity.

This report describes two pairs of sibs presenting with neonatal respiratory difficulty, resembling the symptoms of asphyxiating thoracic dysplasia (dys-trophy) so closely that one family was previously reported as having that condition (Karjoo *et al.*, 1973). The osseous diagnosis became clear only in the second to third year of life. Susceptibility to infection was extremely severe in the other family (lethal in one child).

Case report

Family 1. This family has been reported previously (Karjoo *et al.*, 1973), but additional data on the second sib is now available. The parents are unrelated and

healthy. After two spontaneous abortions 2 sons with metaphyseal chondrodysplasia, malabsorption, and neutropenia were born.

Case 1. The older, more severely affected boy suffered severe progressive respiratory insufficiency because of short ribs and chest deformity. Reconstructive thoracic surgery was performed at age 10 months with improvement of respiratory function.

At age 15 months investigation of continual poor weight gain and diarrhoea showed steatorrhoea (21 g faecal fat/24 h) and markedly diminished pancreatic exocrine response to secretin stimulation. White blood count was 7100/mm³ with 6% polymorphonuclear cells. Small intestinal biopsy was normal. Skeletal x-rays showed short ribs with flaring at the costochondral junction (Fig. 1). The pelvis, hands, and long bones remained normal. Kidney function was normal as determined by intravenous pyelogram and urine analysis. He is now 5 years old and has continued to grow, with height and weight at the 3rd centile.

Case 2. The 4-year-old sib of Case 1. At 2½ weeks of age skeletal x-rays showed narrowed chest with shortened ribs, flared at the costochondral junction (Fig. 2). During the first 10 months of life there was no respiratory distress and white blood count and repeated stool trypsin determinations were normal. Growth failure, neutropenia, and a renal infection were found at 12 months of age. Retesting at this age showed no tryptic activity in the stools. Antibiotics, pan-

FIG. 1.—Case 1. Lateral view of spine at 3 months of age, showing short ribs with widely flared costochondral junctions, and ovoid vertebral bodies.

creatic replacement therapy, and a medium chain length triglyceride formula were started.

Since one year of age he has had repeated otitis

(a)

(b)

FIG. 2.—Case 2. X-rays taken at 2 weeks of age, showing (a) short ribs with flared anterior ends, (b) short, broad femora with slightly flared metaphyses.

media and has maintained a persistent neutropenia (600–800 polymorphonuclear cells/mm³). Tryptic activity was still lacking in duodenal secretions at 3 years

of age. Quantitative immunoglobulins have been normal. He has continued to grow in height and weight at the 3rd centile.

Family 2. The Irish-born Australian parents were unrelated and healthy. Four pregnancies have produced a normal girl, 2 affected boys, and another healthy girl, in that order.

Case 3. Born at term after a normal pregnancy, weighing 3.01 kg. He developed respiratory distress on the second day of life and was noted to have an abnormally short and narrow chest and short limbs with redundant folds of skin over the proximal segments of limbs. An inspiratory stridor was also noted and direct laryngoscopy showed floppy arytenoid cartilages. Dyspnoea was a problem for 3 to 4 weeks, but he was gradually able to suck adequately and to be cared for at home where the respiratory distress steadily improved. His growth followed the 3rd centile. Lung function studies showed a low tidal gas volume (18.4 mg/kg) at 4 weeks, but normal results at 14 weeks.

At 7 months of age a respiratory infection was treated with antibiotics. Swollen cervical lymph nodes developed and an overlying cellulitis spread rapidly to extend beyond the clavicles over the next 24 hours before he died in another hospital. *Proteus mirabilis* was grown from post-mortem blood cultures and from the cervical cellulitis.

The only blood examination performed (day 6) showed haemoglobin 19.1 g/dl, white cell count

5400/mm³ (2% band forms, 8% neutrophils, 68% lymphocytes, 21% monocytes, 1% eosinophils). Unfortunately the neutropenia did not attract any attention. Pancreatic function was not studied nor was a sweat test performed.

Skeletal x-rays taken in the first week (Fig. 3) showed very short ribs with cupped anterior ends, a mild general delay in ossification and ovoid vertebral bodies. The ilia were normal, thus excluding asphyxiating thoracic dysplasia. In later films (including some taken after death at 7 months) rib shortening was less marked, but the metaphyseal plates of the proximal femora had become irregular.

Necropsy showed markedly abnormal ossification with very poor vascularization of epiphyseal cartilage, irregular columnation of chondroblasts, and fibroblastic proliferation across the edge of the epiphyseal plate. The

(a)

(b)

FIG. 3.—Case 3. X-rays of (a) chest at 3 days anteroposterior, and (b) spine at 6 days, lateral showing very short ribs with flared costochondral junctions and ovoid vertebral bodies.

marrow was hypocellular and especially deficient in myeloid precursors.

The liver was mildly fibrotic with severe fatty change and scattered cells with golden cytoplasmic pigment. Inflammation of portal tracts was entirely mononuclear as was that of the hypocellular lymph nodes. Thymus and lymph nodes were otherwise structurally normal.

A necrotic skin lesion showed many bacteria but no polymorphs and the lung exudate was also free of polymorphs. The pancreas was moderately fibrotic (inter- and intralobular) with some loss of exocrine tissue. The islets were hyperplastic.

Case 4. Also born at term after a normal pregnancy and delivery, weighing 3.45 kg, length 50 cm with span 52.5 cm, pubis to heel 19 cm, head circumference 35.5 cm. Respiratory distress, a small chest, and short limbs were apparent immediately. The dyspnoea was less severe than in the brother and he was soon able to suck adequately. While in hospital immunological functions were investigated, since his brother's final illness suggested defective resistance to infection. Immunoglobulins and lymphocyte function tests were normal, but neutropenia was discovered and soon progressed to virtual aneutrocytosis. Results of blood examinations at critical points in his medical history are shown in Fig. 4. Overall his white cells have been counted on 86 occasions, with <1000 neutrophils/mm³ on 72 occasions (<500 on 43 occasions). No cyclical pattern has developed, but monocytosis up to 20% has been noted. The highest neutrophil counts occurred at the times of fresh infections.

During the 36 months of his life he has been admitted to hospital with infections on 7 occasions (Fig. 4).

FIG. 4.—Case 4. Diagram of selected neutrophil counts (cells/mm³). (A) aged 1 day, first presentation with respiratory distress and stridor; (B) 3½ months, when perianal abscess had been present for 1 week; (C) 5 months, episode of perianal cellulitis; (D) 7 months, episode of perianal cellulitis; (E) 9½ months, episode of diarrhoea for 2 days; (F) 11 months, episode of vomiting; (G) 17 months, operation on perianal fistula; (H) 20 months, episode of vomiting, fever, and diarrhoea for 2 days.

Most of the illnesses have been minor, especially as he has grown older, but several were severe and one was almost lethal. At 3 months he was admitted with moderate acute watery diarrhoea. No antibiotics were given and the diarrhoea subsided. He then became acutely ill with peripheral circulatory failure and a rapidly extending perianal cellulitis. Within a few hours the whole anal canal became gangrenous. *Pseudomonas pyocyanea* was cultured from tissue fluid aspirated from the cellulitic area, and *Esch. coli* was grown from a blood culture. He improved with intravenous fluids and gentamicin and a colostomy was performed to divert the faecal stream. Two small patches of gangrenous cellulitis were found in the sigmoid colon. Otherwise the infection was confined to the anal canal which subsequently separated as an eschar. Over the next 6 to 12 months he had repeated recrudescence of cellulitis in the perianal tissues, but each episode settled easily with appropriate antibiotics and the patency of the anal canal has now been re-established by repeated dilatation. The colostomy has been closed subsequently.

During the last 12 months he has been in good general health most of the time and has grown well. His height is currently at the 3rd centile and his weight at the 25th centile.

Skeletal x-rays taken in the newborn period showed a greater delay in ossification than was seen in the brother, though the ribs were not quite as short. Anterior cupping of rib ends was present and the vertebrae were ovoid. By 4 months of age some irregularity of the proximal metaphyses of the femora and humeri was seen. At 12 months (Fig. 5) these sites still showed the greatest abnormality but changes had also developed in the distal femoral metaphyses.

Pancreatic function studies were performed at 3 months because this syndrome was suspected. There had been no suggestive symptoms. Decreased levels of lipase (7.5 μ mol/ml) and trypsin (10.8 μ mol/ml) were shown. He has therefore been treated with pancreatic enzyme replacement and was fed on a medium-chain triglyceride milk (Triglyde, Mead Johnson).

Discussion

One patient in each family clearly possesses the characteristic triad of features of metaphyseal chondrodysplasia, neutropenia, and pancreatic insufficiency. The second sib in each family has sufficient features to accept that they also have the same condition. Autosomal recessive inheritance has seemed likely in the previously reported families and would adequately explain the present families. Chance might account for the fact that all 4 were male, and neither family history gives any other reason for suggesting X-linked inheritance.

These families show that metaphyseal chondrodysplasia can cause rib shortening sufficient to produce respiratory distress in the newborn period,

FIG. 5.—Case 4. Aged 12 months. X-rays of right arm and right leg showing widening and irregularity of the metaphyseal regions.

that radiological confirmation may be impossible before 12 months of age, and that life-threatening infections may occur, especially rapidly spreading cellulitis.

If the immediately lethal bone dysplasias like achondrogenesis and thanatophoric dwarfism are excluded, most babies who present with dyspnoea caused by a small rib cage will prove to have asphyxiating thoracic dysplasia (ATD) (Jeune, Béraud, and Carron, 1955; Maroteaux and Lamy, 1968; Langer, 1968) or the Ellis-van Creveld syndrome (Ellis and van Creveld, 1940; Ellis and Andrew, 1962; Kozlowski *et al.*, 1972). Achondroplasia may rarely present in this manner. These

three conditions may be diagnosed in the newborn period by the radiological changes present in the spine, pelvis, and long bones (Kaufmann and Kirkpatrick, 1974). However, it may be very difficult to distinguish between ATD and the Ellis-van Creveld syndrome (Kozlowski *et al.*, 1972).

Unfortunately, the terms asphyxiating thoracic dysplasia and thoracic asphyxiating dysplasia have also been applied in a loose descriptive fashion to patients with short ribs and dyspnoea who do not have the specific condition described by Jeune and later defined by Maroteaux and Lamy (1968) and by Langer (1968). In a recent review, Jéquier, Favreau-Ethier, and Grégoire, (1973) refer to a number of patients with 'ATD with normal pelvis' most of whom had not been followed to the age when cone-shaped epiphyses (the other key feature of ATD) might be seen in the hands. Some of these patients may have metaphyseal chondrodysplasia. However, metaphyseal chondrodysplasia does not explain all currently undiagnosed babies with small thoraces. Mild variants of ATD do occur and other self correcting conditions appear to exist (Danks *et al.*, in preparation).

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