Asphyxiating Thoracic Chondrodystrophy
Association with Renal Disease and Evidence for Possible Heterozygous Expression

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Asphyxiating thoracic dystrophy of the newborn is a rare skeletal abnormality. Though the disease is generalized in distribution, the cartilaginous thoracic cage bears the brunt, with the results that the chest is narrow and immobile. The outcome is usually fatal early in the neonatal period. Less frequently the patients survive with severely impaired respiratory function only to succumb to repeated and ultimately fatal respiratory infections. The entity was first described by Jeune et al. (1954) who observed it in two sibs. Subsequently, nine more cases were reported in the European literature (de Sario and Marchese, 1956; Balocco and Zoratto, 1960; Neumann et al., 1963; Maroteaux and Savart, 1964; Fontan et al., 1965). Only recently has the entity been observed by American investigators; Pirnar and Neuhauser (1966) published the first report of the condition in the English language literature.

The clinical and radiological features were comprehensively reviewed by Hanissian, Riggs, and Thomas (1967) and Langer (1968). The familial distribution has been noted and autosomal recessive inheritance suggested. In this paper we present a large pedigree with five subjects either affected or reputed to be affected with this syndrome.

Case Reports

IV.17 (Fig. 1). This male infant was born at term in 1969 with birthweight 3125 g. and length of 49 cm. The antenatal history was unremarkable. Severe respiratory distress was immediately apparent at birth, and since there was no improvement he was transferred at 12 hours of age from the local hospital to the University Hospital in Saskatoon. Admission examination revealed a deeply cyanotic infant with constricted chest and extreme limitation of thoracic movement. On auscultation air entry was virtually absent but the heart sounds were normal. The abdomen was bulging with the liver felt 4 cm. and spleen 1 cm. below the costal margin. Both kidneys were palpably enlarged with firm consistency. The skin, hair, fingers, and nails appeared normal. There were bilateral simian palmar creases and the upper arms and thighs were shorter than normal. Despite energetic treatment he died in deep cyanosis at 33 hours of age.

Radiology. (Fig. 2). The lungs were almost completely opaque. The ribs were broadened anteriorly and were very short, resulting in an extremely small thoracic cage in both diameters. Each scapula was small and rather square with marked irregularity of the glenoid. Considerable gas was present within the stomach and bowel. The skull was unremarkable. The vertebral bodies were normally ossified and there was no narrowing of the interpedicular distances in the lower lumbar spine.

Each humerus was slightly shorter than normal but the radius and ulna were unremarkable. The metacarpals and phalanges were somewhat short. The iliac bones showed an almost square configuration being very wide in relation to their height, with a very shallow sciatic notch and a very flat irregular acetabular angle. Each femur was short, rather wide, and slightly bowed with some irregularity of the ends. The ossification centres were unusual since they had already appeared for the proximal femur and the proximal humerus (not expected until 3 and 1 months of age respectively), whereas the centres at the distal femur and proximal tibia had not yet appeared (these should have appeared at 36 and 40 fetal weeks, respectively). Each tibia and fibula were somewhat short.

The narrow thoracic cage, configuration of the ribs, scapulae, and iliac bones, slight shortening of the long bones, and precocious appearance of the centres for the proximal femur and humerus were quite typical of asphyxiating thoracic dystrophy.

Necropsy. A male infant with bilateral depression of the chest wall at the costochondral junctions (Fig. 3). Internally, bossing of the costochondral junctions gave a typical 'rosary' appearance. Chest capacity below the nipple level was much diminished with compression of both lungs. The lungs themselves were somewhat hypoplastic and patchily collapsed with failure of lobation on the left and only beginning of lobation on the right.

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The kidneys showed persistent fetal lobulation and their cortical surfaces were studded with numerous cysts. There was stenosis at each ureterovesical junction with moderate hydroureter. The heart was unremarkable but the liver showed patchy areas of coarse wrinkling of Glisson's capsule.

**Microscopical examination.** Though the lungs appeared hypoplastic on gross inspection histological maturity was appropriate for age. There was evidence of congestion, alveolar haemorrhage, incomplete aeration, and early acute bronchopneumonia. In the brain, early anoxic change was noted in the sensitive sector of Ammon's horn. The liver sinusoids were much congested. An interesting finding was the presence of

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FIG. 1. Pedigree of a family with asphyxiating thoracic dystrophy.

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FIG. 2. X-ray of IV.17.

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FIG. 3. Post-mortem photograph of IV.17 showing constricted chest and bulging abdomen.
hyperplastic activity of portal bileducts without any evidence of cholestasis (Fig. 4). The bile-duct system was patent throughout. The renal cysts were due to cystic distension of convoluted tubules especially along the subcapsular zone. Sometimes one could see flattened glomeruli within the distended Bowman’s capsules (Fig. 5). In some areas, glomerular sclerosis, atrophy, or capsular fibrosis was seen. In the deeper cortex, cystic distension of the distal convoluted tubules also became apparent, but the collecting system was very little affected. These renal changes were in keeping with Potter’s Type IV polycystic kidney (Osathanondh and Potter, 1964).

In the skeletal system, the humeral heads, scapulae, vertebrae, and many ribs were histologically studied. Though they were all affected, the scapulae and ribs were most severely involved. The articular surface of the glenoid fossa of the scapula was smooth and the underlying chondrocytes were fairly orderly; however, along the physis and metaphysis the endochondral ossification was completely disorganized. Columnation of chondrocytes was irregular and cell vacuolization poor (Fig. 6). The ossification line showed a zig-zag pattern occasionally having one or two islands of cartilaginous tissue in the metaphysis or interdigitating with areas of early primary spongiosa formation. Along the physis, the areas with hypertrophic chondrocytes showed a focal, far advanced ossification process, while failure or retardation of the ossifying process was seen distal to the areas of atrophic chondrocytes. The ribs showed a similar defective endochondral ossification causing a sliding effect of the cartilage and resulting in subluxation of the costochondral junction. The upper ends of the humeri and the vertebrae had similarly defective ossification but to a lesser degree.

IV.16 (Fig. 1). This female infant was born at term in 1968 with birthweight 3070 g. Antenatal history was unremarkable. In spite of active attempts at resuscitation, she never breathed, though her heart continued to beat for some hundred minutes after birth. The chest was stenotic and collapsed with short wide ribs and enlarged costochondral junctions with palpable rosary formation. Enlargement of the abdomen was noted with the liver 5–6 cm. below the costal margin. Both kidneys were palpably enlarged. Apart from cyanosis, her skin was normal as were fingers, nails, and hair. No necropsy was performed, but a radiograph was taken which is almost identical to Fig. 2.

IIIa.5 (Fig. 1). This infant is a first cousin once removed (one and a half cousin) of IV.17 and IV.16. As reported by the attending physician she was born at term but lived only a few days, experiencing respiratory difficulty throughout and was cyanotic at the time of death. She is said to have had a small contracted chest and bulging abdomen.

IIIa.6 and 7 (Fig. 1). These infants were female twins of unknown zygosity and sibs to IIIa.5. They were born at 41 weeks’ gestation and both had extreme difficulty with breathing. They remained cyanotic with asphyxia as the apparent cause of death. IIIa.16 survived 16 hours and IIIa.17 only 12 hours after birth. Both had narrow constricted chests with bulging abdomens.
asphyxiating thoracic dystrophy. It is noteworthy, however, that renal disease was found to be associated with this disorder in at least three cases (Herdman and Langer, 1968; Wiedmann, 1966). In those patients, the affection manifested as renal failure, hypertension, and death in uraemia. Necropsy specimens of renal tissue were available only in one case (Herdman and Langer, 1968) and microscopy showed 'predominantly interstitial fibrosis, round cell infiltration, and tubular atrophy and dilation'. The picture reported is not unlike that seen in nephrophthisis or Alport's syndrome. Moreover, though hepatic lesions are known to occur occasionally in association with renal cystic disease, hyperplasia of portal bileducts, as seen in IV.17, has never before been described in thoracic dystrophy.

Since necropsy was done on only two other cases among those so far reported in the literature, with no comment in either on the condition of the kidneys or ureters, it is conceivable that malformations such as those encountered in IV.17 were overlooked or never detected. Investigators may be urged to search for such anomalies in future cases.

Unlike those reported by Hanissian et al. (1967), our cases did not show evidence of ectodermal dysplasia. The claim voiced by these authors that asphyxiating thoracic dystrophy should be considered a variant of Ellis Van Creveld syndrome could not be substantiated in our cases. The long survival of some of their patients, which has not been demonstrated previously or since, leads us to question the validity of assigning this nosological entity to their cases. Indeed it is likely from the clinical description given in their paper that their cases constitute examples of Ellis Van Creveld syndrome. No useful purpose seems to be served by confusing two patently distinct clinico-pathological entities.

Both parents IV.17 and IV.16 are of Norwegian descent and have been in this continent for only one generation. However, no definite consanguinity could be ascertained. Before the birth of their two affected offspring, the parents had a normal child (VI.1, Fig. 1). In view of the fact that the parents are free of this ailment, had a normal child, and the affected sibs were of unlike sex, little doubt is entertained that autosomal recessive transmission is the operating mode of inheritance. This conclusion seems to be borne out when all the previously reported cases in the literature were reviewed with a view to the elucidation of the possible mode of their inheritance.

Furthermore, three sibs (IIIa.5, 6, and 7) who were first cousins to the mother of IV.17 and IV.16,
died shortly after birth from apparently the same condition. Though their parents are also of Norwegian extraction, neither consanguinity nor relation to IIIb.11, Fig. 1) could be established.

It is perhaps noteworthy that a maternal uncle of IV.17 and IV.16 suffers from a noticeable chest deformity, namely, pectus excavatum and anterior depression of the left hemithorax. Though susceptible to repeated respiratory infections during infancy and childhood, he now appears in a functionally satisfactory condition and has recently been admitted to the Armed Forces. Having an a priori probability of one in two of carrying the abnormal allele, his chest deformity may represent partial expression in a heterozygote. Moreover, the father (II.15) and an elder sister (IIIa.4) of cases IIIa.5, 6, and 7 have deformity of the chest and, in the former case, also of both hands and feet (short stubby metacarpal, metatarsal, and phalangeal bones). Their probabilities of being heterozygotes are one and one in two respectively. It is possible that relatives of index cases who show only deformity of the chest and/or hands and feet may represent mild expression in heterozygous carriers, with only homozygotes suffering the full-fledged asphyxiating form.

**Summary**

A family with 5 subjects (two sets of sibs) who were affected with asphyxiating thoracic dystrophy is presented. The disease proved fatal in all instances shortly after birth. Our objectives in communicating this paper have been (1) to introduce the entity to medical genetics' literature, (2) to point out the mode of inheritance, namely, autosomal recessive transmission, (3) to call attention to the abnormality in the urinary system, which may prove to be an integral part of the syndrome, and (4) to suggest the possibility of heterozygous expression as deformity of the chest.

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*Fig. 6.* Low power view of the glenoid displaying defective vacuolization and cullomation of chondrocytes. (H. and E. × 40.)
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