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Congenital muscular dystrophy associated with lethal arthrogryposis multiplex congenita

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Summary. Two unrelated patients with severe arthrogryposis multiplex congenita (AMC) who died perinatally, are presented. In both, postmortem examination revealed an intact nervous system and striking dystrophic muscle changes, consistent with congenital muscular dystrophy (CMD). Few similar cases have been reported before, but since the condition is not well known, it seems probable that in the past many have been labeled as mere multiple malformations. The possibility of an underlying muscular disorder, either primary myopathic or neurogenic should be considered in any patient with early lethal AMC.

Our findings confirm that the fetal akinesia-arthrogryposis sequence is a nonspecific clinical syndrome resulting from various causes of muscular inactivity in utero. The main objective of this report is to provide reasonable guidelines on how to approach the problem of classification. We favor a pathogenetic approach, depending upon careful sampling of the central nervous system and skeletal muscles at autopsy.

Key words: Arthrogryposis – Congenital muscular dystrophy – Perinatal autopsy

Introduction

Neonatologists and pediatric pathologists are occasionally confronted with infants expiring shortly after birth, with multiple joint contractures ("arthrogryposis") generalized muscle wasting and pulmonary hypoplasia. Such cases are frequently dismissed as multiple congenital malformations. However, over-interpretation of the symptom complex as a specific disease entity is another diagnostic pitfall. In fact, the clinical features of this "syndrome" are nonspecific and should be regarded as a malformation sequence, often

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secondary to an underlying neuromuscular defect with severe "fetal akinesia" (Smith 1982; Hall 1984). Therefore, dissection and histological examination of the central nervous system (including the spinal cord) and extensive muscle sampling are of paramount importance in the practical approach to such cases. Only in this way can the basic pathological process be elucidated, allowing correct genetic counseling.

We present two unrelated patients with the clinical picture of severe AMC, who died immediately after delivery in extreme respiratory distress. Postmortem examination revealed CMD in the presence of an intact central nervous system.

Case reports

Patient 1. This boy, born prematurely at 32 weeks' gestation, was the product of the fifth pregnancy of a 27-year-old mother and a 26-year-old father. Pregnancy was complicated by polyhydramnios, and the mother experienced diminished fetal movements. The parents are second cousins. The first and third pregnancy ended with an early spontaneous abortion. Two other male children are alive and well.

Shortly after birth, the infant died of respiratory dysfunction. The body weight was 1,195 g, the crown-rump length 24.5 cm, and the head circumference 29.5 cm. Clinically, multiple joint deformities were evident, and the muscle mass of the extremities was reduced (Fig. 1). Shoulder abduction was very restricted, the elbows were fixed in flexion and the wrists in dorsiflexion. The hands displayed camptodactyly, clinodactyly, and virtually absent palmar creases and dermal ridges. The hip joints were strongly flexed, the knees extended, and the feet showed severe equinovarus deformities bilaterally. The face exhibited hypertelorism, a high-arched palate and slight micrognathia. X-ray examination demonstrated marked thoraco-lumbar scoliosis, convex to the right.

Autopsy revealed striking pulmonary hypoplasia (combined lung weight 8.0 g, lung weight/body weight ratio 0.0067). The brain and spinal cord were normal, both grossly and microscopically. Muscle samples of all the extremities, diaphragm and intercostal muscles were examined after Bouin fixation. Haematoxylin-eosin, Masson trichrome, and phosphotungstic acid haematoxylin stains were used. All muscles showed a myopathic pattern with partial fatty replacement. The muscle fibres varied markedly in diameter. Small atrophic fibres alternated with large hypertrophic ones. Transverse sections disclosed rounding of the muscle fibres and many centrally placed nuclei. Some fibres displayed hyalinization of the sarcoplasm. In addition there was focal necrosis with phagocytic reaction. The endomysial connective tissue was markedly increased. The intramuscular nerve fibres and muscle spindles appeared normal. Inflammation was absent but areas of extramedullary hematopoiesis were frequently seen. There was only slight variation in the severity of the process in different muscles. Postmortem degeneration impaired adequate interpretation of the enzyme histochemical studies.

Cytogenetic examination revealed a normal 46, XY male karyotype, confirmed by G- and Q-banding.

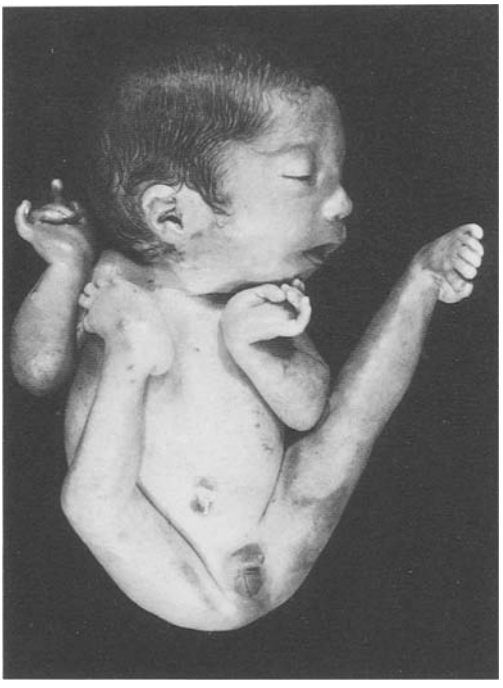


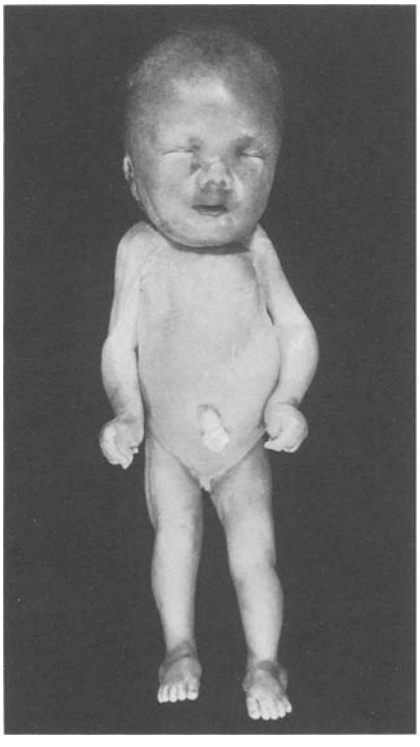
Fig. 1. Patient 1, exhibiting the etiologically nonspecific clinical features of lethal AMC ("fetal akinesia syndrome")

Patient 2. This girl was the first child of healthy and unrelated parents aged 24 years. The pregnancy was complicated by polyhydramnios and ended prematurely at approximately 30 weeks' gestation. The mother was Rh negative but laboratory tests showed no rise in antibody titre. She had no previous abortions. Delivery was unremarkable but the child made no spontaneous respirations. She died aged 1 h.

Physical examination revealed a 1,070 g female infant with a crown-foot length of 34.0 cm, and a head circumference of 27.5 cm (Fig. 2). There was moderate soft tissue oedema. The face exhibited hypertelorism and retrognathia. The arms were held straight along the body with the elbows fixed in extension and the wrists in dorsiflexion. There was marked campto- and clinodactyly of the fingers. In addition, the hands showed hypoplastic palmar creases and dermal ridges. The lower limbs were fixed in extension. The feet displayed rigid flexion contractures of the toes. X-ray examination disclosed a thoracic scoliosis with convexity to the right, and hypoplasia of the right acetabulum with dislocation of the right hip.

Autopsy demonstrated borderline hypoplasia of the lungs (combined lung weight 13.0 g, lung weight/body weight ratio 0.012). The brain exhibited a massive subarachnoid haemorrhage at the base of the left temporal lobe. No further central nervous system abnormalities could be detected either grossly or microscopically. Muscle samples showed severe dystrophic changes, identical to those described in case 1 (Fig. 3).

Chromosomal analysis revealed a normal 46, XX female karyotype, confirmed by G- and Q-banding.



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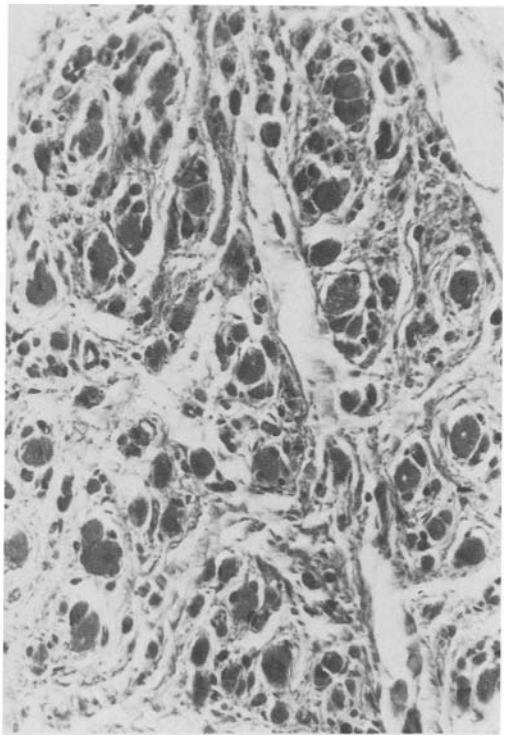

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Fig. 2. Patient 2

Fig. 3. Intercostal muscle biopsy in patient 2, showing striking dystrophic changes. (Masson trichrome; ×350)

Discussion

The name "arthrogryposis", signifying "curved joints", was coined by Rosenkranz in 1905. In 1923 Stern extended this term to "arthrogryposis multiplex congenita". AMC was initially an orthopedic diagnosis applying to the condition of multiple joint contractures present at birth. It is now clearly established that AMC is an aetiologically nonspecific symptom complex that can be caused by a variety of pathogenetic mechanisms. The congenital articular rigidities are due to fibrosis of the joints and contiguous structures, resulting from early intrauterine immobilization. Impairment of fetal joint movements can be attributed to oligohydramnios giving rise to mechanical compression, or can be the result of a primary skeletal or connective tissue abnormality, e.g. diastrophic dwarfism, Larsen syndrome (Houston et al. 1981). However, the fundamental mechanism responsible for most cases of AMC is a neuromuscular disorder, either neurogenic or myopathic.

AMC can be severe, leading to stillbirth or early neonatal death. In addition to multiple joint contractures, generalized muscle wasting and pulmonary hypoplasia, intrauterine growth retardation is usually present and

pregnancy is complicated by polyhydramnios and decreased fetal movements. Physical examination often shows a rigid expressionless face with some degree of micrognathia and hypoplasia of palmar creases and dermal ridges on the hands and fingers. Fetal akinesia syndrome (Hall 1984) is indeed a very appropriate designation for this condition. Some of these infants have spinal muscular atrophy (Brandt 1947; Drachman and Banker 1961; Vestermark 1966). Histologically, the muscles show denervation atrophy and there is a loss of anterior horn cells in the spinal cord. These features have been well-documented in the Pena-Shokeir I syndrome (Moerman et al. 1983). We propose that the latter term should strictly be reserved to those cases in which spinal muscular atrophy has been confirmed at autopsy. Some cases of neurogenic AMC are associated with malformations of the brain. Fowler (1959) pointed out that in these patients the abnormality of the anterior horn cells can be the result of a developmental defect, contemporaneous with that of the brain, or can be an example of transsynaptic atrophy, consequent to the loss of large pyramidal cells in the precentral gyrus or to degeneration of the pyramidal tracts. The pyramidal tracts are absent in anencephalic infants, while the musculature is normally developed.

CMD is a congenital myopathy. Although Howard had already described a case of "dystrophia muscularis congenita" as long ago as 1908, the condition is relatively unknown. Familial cases have been reported, but it is not certain whether it is genetically distinct. The clinical course is very variable. Hypotonia, muscle weakness and usually joint contractures are present from birth (Dubowitz 1978). Since 1960, several publications, mostly from Japan, reported developmental central nervous system abnormalities in infants with CMD. This separate entity has become known as Fukuyama type cerebro-muscular dystrophy (McMenamin et al. 1982). CMD must be differentiated from neonatal myotonic dystrophy (Steinert's disease). The latter is characterized histologically by a diffuse "immature" aspect of the muscle tissue. All fibres remain abnormally small and round, often containing a large, vesicular central nucleus. Longitudinal sections show periodic chains of central nuclei with clear vacuolated internuclear spaces. There is no muscle necrosis or degeneration (Sarnat and Silbert 1976).

We described two infants with severe AMC dying of respiratory failure in the neonatal period. In both, the central nervous system was normal at autopsy, but the muscles showed striking dystrophic changes. Only a few similar cases have been reported in the literature. Of the two siblings described by Banker et al. (1957), the second died one and a half hours after birth with kyphoscoliosis and hypotonic flaccid weakness. A sibling of case 1 described by Zellweger et al. (1967) died at the age of three months of arthrogryposis and muscular dystrophy. One other patient is illustrated by Wigglesworth (1984). These observations and ours indicate that severe muscular dystrophy of prenatal onset is the underlying defect of at least some cases of severe fatal AMC. Sporadic cases, such as ours, present a problem for genetic counseling. The congenital dystrophic myopathy could be genetically determined or acquired (in utero myositis due to Influenza

A or Coxsackie infection for example). To our knowledge, no simple criteria exist for making such distinctions.

The polyhydramnios is most probably due to inadequate swallowing of amniotic fluid. Pulmonary hypoplasia is secondary to involvement of the diaphragmatic and thoracic wall musculature. In this context, it is also worth mentioning that pulmonary hypoplasia resulting from congenital relaxation or eventration of the diaphragm can be the dominating feature in infants with a severe congenital muscular or neuromuscular disease (Bossen et al. 1974).

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