Lethal olivopontoneocerebellar hypoplasia with dysmorphic features in sibs

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Abstract

This report describes the clinical and neuropathological features in male and female sibs who died shortly after birth as a result of frequent convulsions and lack of spontaneous respiratory effort. Both sibs had a prominent occiput with mild contractures and the female also had overlapping fingers and rockerbottom feet. The genetic and neuropathological findings were consistent with a diagnosis of an autosomal recessive form of olivopontoneocerebellar hypoplasia/atrophy.

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Hypoplasia of the cerebellar hemispheres in association with underdevelopment of the pons ('pontoneocerebellar hypoplasia') was described in 1958 by Norman and Urich¹ in two unrelated children, both of whom died during the first year of life. The parents of one of these children were second cousins, an observation suggestive of autosomal recessive inheritance. Recessive inheritance was also proposed as the probable mode of inheritance in male and female sibs who died in early childhood with a diagnosis of congenital 'olivopontocerebellar atrophy',² and in seven cases described in five Dutch families.³ We have recently encountered a further sibship in which two babies died shortly after birth with a particularly fulminant form of familial olivopontoneocerebellar hypoplasia. One of these infants also had a number of dysmorphic features.

Case reports

The affected sibs were the products of the first

two pregnancies of young, healthy, unrelated, Caucasian parents who had no history of relevant hereditary disease.

CASE 1

Concern first arose at 34 weeks' gestation when the mother noticed a reduction in fetal movements which coincided with the onset of polyhydramnios. Two weeks later after spontaneous onset of labour, she delivered a female infant weighing 1490 g (<3rd centile). Body length was 39.5 cm (<3rd centile), and head circumference 27.2 cm (<3rd centile). The baby made no attempt to breathe spontaneously, had frequent convulsions, and died at the age of 24 hours.

Abnormalities noted during life included a prominent occiput, micrognathia, and contractures of all four limbs with overlapping clenched fingers and bilateral rockerbottom feet (fig 1). At necropsy the total brain weight was 140 g (expected weight = approximately 350 g), and in particular the hind brain was disproportionately small weighing only 2 g (expected weight = 20 g) (fig 2). The lungs were in proportion to the body size and no visceral abnormalities were present. Chromosome studies using cultured lymphocytes showed a normal female karyotype.

CASE 2

This pregnancy was monitored regularly using ultrasonography from 16 weeks onwards. No abnormalities were noted until 34 weeks' gestation, when, as in the first pregnancy, polyhydramnios developed in association with a reduction in fetal movement. At 36 weeks an intrauterine convulsion was observed. At delivery three days later the male infant weighed 2010 g (3rd centile), length 46 cm (50th centile), and head circumference 29.5 cm (3rd centile). Once again the baby made no spontaneous respiratory effort, showed frequent convulsive activity, and died at the age of 48 hours.

Dysmorphic features were less apparent in this baby than in his affected sister (case 1), and consisted of mild contractures in all limbs with a prominent occiput, receding forehead, and micrognathia (fig 3). A CT scan showed cerebellar hypoplasia with cerebral atrophy. These findings were confirmed at necropsy. Total brain weight was 104 g (expected for gestational age = 366 g) and the hindbrain again was disproportionately small at 2.8 g (expected weight = 21 g). No other abnormalities were detected on internal examination.

Figure 1 Case 1 shortly after birth. Note the overlapping 'trisomy 18' fingers and rockerbottom feet.

Figure 2 The brain of case 1 showing marked hypoplasia of both cerebellar hemispheres.

NEUROPATHOLOGY

Sections of the brains of both sibs showed similar changes with most severe involvement of the brainstem and cerebellum. There was marked loss of neurones with reactive astrogliosis in the pontine nuclei. The transverse fibres of the pons were depleted. The inferior olivary nuclei also showed neuronal loss and gliosis. Pyramidal tracts were normal. The cerebellum showed loss of Purkinje cells and depletion of the internal granular layer in the hemispheres. The external granular layer was reduced in thickness but still identifiable. The vermis, floccules, and nodules (components of

Figure 3 Postmortem view of case 2. Note the pointed occiput.

the archi- and paleocerebellum) were well preserved. The dentate nuclei retained their normal outline but showed severe neuronal loss and reactive gliosis.

Sections of the cerebral hemispheres showed no evidence of malformation. The cortex was normally laminated. Neuronal necroses were seen in the hippocampus and subiculum and there was gliosis and macrophage infiltration in cerebral white matter, consistent with recent ischaemia or hypoxia.

The spinal cord showed normal anterior horn cells with normal and symmetrical anterior and posterior nerve roots.

Discussion

The clinical features shared by these sibs included relative microcephaly, prominent occiput, micrognathia, and contractures. In addition, case 1 had overlapping fingers and rockerbottom feet which initially suggested a possible diagnosis of trisomy 18. Neurologically their disease ran an almost identical course marked by reduction in fetal movement and polyhydramnios, presumably a manifestation of impaired deglutition, from 34 weeks onwards, with subsequent convulsions and failure to develop spontaneous respiration at birth. At necropsy both had severe cerebellar hypoplasia and neuropathological studies showed olivopontocerebellar hypoplasia.

The initial diagnosis of trisomy 18 in case 1 was rapidly refuted by the discovery of a normal karyotype. Alternative diagnoses which were considered included the Pena-Shokeir and Bowen-Conradi syndromes. The Pena-Shokeir syndrome is generally accepted as being extremely heterogeneous, representing the phenotype resulting from long standing fetal akinesia.⁴ Cerebellar hypoplasia has been noted in a small proportion of published cases⁵ although reduction in anterior horn cells is a more characteristic finding. The absence of pulmonary hypoplasia in the cases now described is consistent with the relatively late onset of reduction in fetal movements (34 weeks), and together these observations suggest that the disease in these infants should not be categorised as falling within the spectrum of the Pena-Shokeir phenotype.

The Bowen-Conradi syndrome is a rare autosomal recessive disorder described mainly in the Hutterites.⁶ The major features are intrauterine growth retardation, microcephaly, micrognathia, contractures, rockerbottom feet, and death in early infancy. The facial profile of children with this condition is very similar to that in case 2 and cerebellar abnormalities consisting of partial agenesis and 'hypoplasia or atrophy' have been noted.⁶ Although this condition is regarded as lethal, the degree of neurological dysfunction is not as severe as in the cases now reported with the most noticeable differences being the achievement of spontaneous respiration and rarity of convulsions in the neonatal period.

The neuropathological demonstration of a small brainstem with hypoplasia of the cerebellar hemispheres suggests that the disorder

in these sibs is best classified as a form of olivopontocerebellar hypoplasia or atrophy. In 1986, Kawagoe and Jacob⁷ reported almost identical neuropathological findings in a female infant who died at the age of 9 days having had generalised convulsions and 'long term apnoea attacks'. The child also had bilateral talipes. These authors proposed that the cerebellar hypoplasia was the primary abnormality and that the absence of nerve cells in the pons and inferior olives was secondary to neuronal deprivation or inactivity. A further case report by Pitella and Nogueira⁸ described a 9 day old male infant with widely separated nipples, overlapping toes, and hypertrichosis of the gluteal and sacrococcygeal regions with pontocerebellar hypoplasia. These authors suggested that the severe neuronal loss and gliosis in the pontine nuclei may represent the primary lesion which is followed by neocerebellar degeneration. Barth *et al*³ reported similar CNS findings in seven children, two boys and five girls, from a Dutch genetic isolate, four of whom died in childhood. Their illness was characterised by congenital and occasionally progressive microcephaly, myoclonic jerks, generalised convulsions, and profound developmental delay. The neuropathological findings in the case examined by Barth *et al*³ were similar to those in our own cases.

Pontocerebellar hypoplasia is a term applied to a group of conditions with a variety of clinical presentations and of heterogeneous neuropathology. In our cases, severe neuronal loss and gliosis in the pontine nuclei, dentate nuclei, inferior olivary nuclei, and neocerebellum suggest a degenerative process occurring after these structures had developed, that is, atrophy rather than primary hypoplasia. The clinical history of reduced fetal movements at 34 weeks of gestation is consistent with relatively late onset of the disorder. The aetiology is diverse and the condition has been associated with both metabolic disease² and anticonvulsant ingestion during pregnancy.^{9,10} These

cases confirm that this appearance may also be the consequence of an autosomal recessive neurodegenerative process.

Note added in proof

A third pregnancy was complicated by polyhydramnios at 32 weeks. A fetal scan showed growth retardation and fixed flexion of one wrist and hand. A male infant was delivered at 38 weeks, birth weight 2760 g, with microcephaly and fixed flexion contractures of the limbs. The heart rate was 40/minute and there were no spontaneous respirations. Resuscitation was not attempted and the infant died aged 10 minutes.

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