Lethal olivopontoneocerebellar hypoplasia with
dysmorphic features in sibs

I D Young, P A McKeever, M V Squier, J Grant

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 effect.
Both sibs had a prominent occiput with
mild contractures and the female also
had overlapping fingers and rockerbot-
ttom feet. The genetic and neuropatho-
logical findings were consistent with a
diagnosis of an autosomal recessive form
of olivopontoneocerebellar hypoplasia/
atrophy.
(J Med Genet 1992;29:733–5)

Hypoplasia of the cerebellar hemispheres in
association with undervdevelopment of the pons
('pontocerebellar hypoplasia') was de-
scribed 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 encoun-
tered a further sibship in which two babies
died shortly after birth with a particularly
fulminant form of familial olivopontoneocere-
bellar 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 rele-
vant 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 sponta-
neously, had frequent convulsions, and died
at the age of 24 hours.
Abnormalities noted during life included a
prominent occiput, micrognathia, and contrac-
tures 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' ges-
tation, when, as in the first pregnancy, poly-
hydramnios developed in association with a
reduction in fetal movement. At 36 weeks an
intrauterine convulsion was observed. At de-
ivery three days later the male infant weighed
2010 g (3rd centile), length 46 cm (50th cent-
ile), and head circumference 29·5 cm (3rd
centile). Once again the baby made no sponta-
neous 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 28 g
(expected weight = 21 g). No other abnor-
malities were detected on internal examination.
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. Cerebellar hypoplasia has been noted in a small proportion of published cases 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. 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. 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

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

**Figure 3** Postmortem view of case 2. Note the pointed occiput.
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in these sibs is best classified as a form of olivopontocerebellar hypoplasia or atrophy. In 1986, Kawagoe and Jacob\(^7\) 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 Nogueira\(^8\) 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 \textit{et al}\(^9\) 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 \textit{et al}\(^9\) 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 disease\(^7\) and anticonvulsant ingestion during pregnancy.\(^8,9\) 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.

The authors are grateful to Dr U M MacFadyen for referring the family.

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J Med Genet 1992 29: 733-735
doi: 10.1136/jmg.29.10.733