Journal of Medical Genetics, 1983, **20**, 210–212

Microcephaly and intracranial calcification in two brothers

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SUMMARY Sibs are reported with severe congenital microcephaly, spasticity, and seizures. Both had extensive intracranial calcification.

The association of microcephaly, mental retardation, seizures, and intracranial calcification is known to be a consequence of infection, especially toxoplasmosis and cytomegalovirus.[1] Rubella and herpes hominis have occasionally been implicated.[2] The occurrence of this combination in sibs has been reported in 'Cockayne's' syndrome[3] and the connatal type of Pelizaeus-Merzbacher disease.[4] Other reported cases do not allow exact classification but most are compatible with a diagnosis of Cockayne's syndrome. The purpose of this paper is to report two sibs with intracranial calcification and severe microcephaly from birth in order to highlight the difficulties for the genetic counsellor.

Case reports

Case 1 was born after a normal term pregnancy and delivery. At birth his head circumference was 32·7 cm (well below the 3rd centile) (fig 1). There were no dysmorphic features. His weight at 3·5 kg was on the 50th centile. By the age of 8 months he had no head control but tone was increased in all four limbs, the reflexes were brisk, and the plantar responses were extensor. His optic fundi were normal. CT scan (fig 2) showed symmetrical dilation of all the ventricles, widening of the cortical subarachnoid space, and extensive calcification in the white matter. To a lesser extent calcification was present in the cerebellum and in the brain stem. The possibility of an antenatal infection was considered His rubella titre was 1/25 and toxoplasma dye test 1/16. The chromosome analysis and the urine amino-acid excretion pattern were normal. From 2 weeks of age he had episodes in which his arms would extend, his legs flex, and his eyes roll upwards. These occurred many times a day. His EEG (Dr Pampiglione) showed a severe abnormality with multifocal discharges. The visual evoked responses and the electroretinogram were normal (Dr Ann Harden). The seizures were not readily controllable and he died from an intercurrent respiratory tract infection at 2 years 3 months of age. No necropsy was allowed.

The unrelated healthy parents requested genetic counselling after the birth of the first affected child. They had a normal girl. In view of the combination of severe retardation, microcephaly, and intracranial calcification, an intrauterine infection was considered, although no confirmation of this was found. A lowish recurrence risk was given. The mother then became pregnant again and the fetal head circumference was measured at 17, 20, and 25 weeks and compared with the abdominal circumference.

Received for publication 20 November 1982.
Accepted for publication 16 December 1982.

FIG 1 *Case 1 with severe microcephaly.*

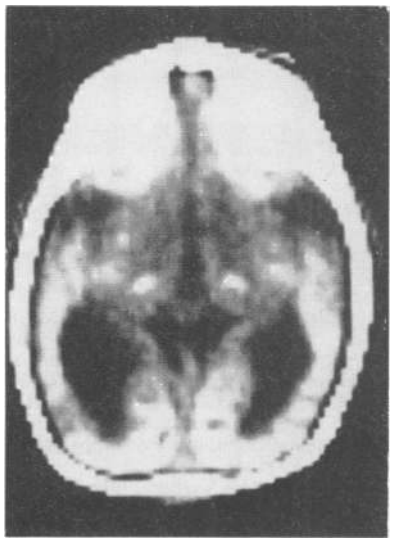

FIG 2 *Case 1 showing extensive intracranial calcification.*

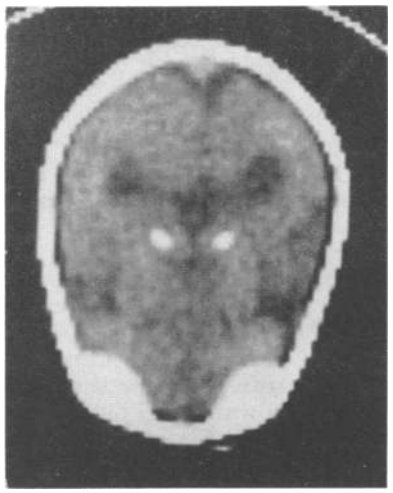

FIG 4 *Case 2 showing extensive intracranial calcification.*

Microcephaly was not detected and the pregnancy proceeded.

Case 2, the brother of case 1, was microcephalic at birth, with a head circumference of 31·5 cm (well below the 3rd centile) (fig 3). The pregnancy was normal and the birth without complications. At term his birth weight was 4 kg. He had no dysmorphic features. CT scan (fig 4) showed moderate dilation of the lateral ventricles and faint bilateral symmetrical calcification of the white matter. Dense nodules of calcification similar to those shown in the brother were present in the thalami. He has had many fits from the age of one month, often six times in quick succession, approximately four to five times a day.

On neurological examination, the tone was increased in all limbs and was more marked in the arms than in the legs. Tendon reflexes were increased and he showed automatic walking at 3 months. The EEG was grossly abnormal, with large amplitudes, irregular slow waves over all regions, and frequent multifocal sharp waves and spikes (Dr Ruth Harris).

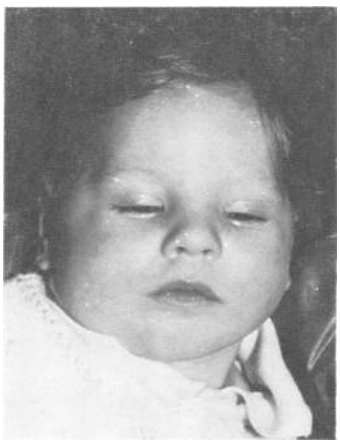

FIG 3 *Case 2 with severe microcephaly.*

Discussion

Microcephaly can be inherited as an autosomal recessive condition. This mode of inheritance should be considered in the presence of a skull circumference more than 3 SD below the norm, in those with large ears and micrognathia, and in the absence of neonatal problems, gross spasticity, and frequent seizures. The two brothers in this report had marked disproportion between the size of the face, which was normal, and the cranial circumference, which was small, but the occurrence of numerous seizures and gross spasticity makes the diagnosis of recessive microcephaly unlikely. On *x*-rays of the skull, the calcification was compatible with a viral infection or toxoplasmosis, but there was no confirmatory evidence for either. With the birth of the second child a genetic syndrome needed to be considered.

There have been reports of sibs with microcephaly, mental retardation, and intracranial calcification. Most of these cases have had Cockayne's syndrome. These include the patients of Laubenthal and Hallervorden,[5] Neil and Dingwall,[6] Norman and Tingey,[7] and Crowe and Kanjilal.[8] Cockayne's syndrome is characterised by initially normal development and microcephaly which is not present from birth. Other features typical of Cockayne's

syndrome, short stature, deafness, retinal changes, progressive neurological deficit, skin sensitivity to sunlight, and progeroid changes, were not present in our two patients.

Jervis[9] in 1954 described two unrelated patients with convulsions, mental retardation, microcephaly (from birth), optic atrophy, and considerable spasticity. No inflammatory lesions were found at necropsy. Calcification was present throughout the cortex but was more conspicuous in the basal ganglia than in other areas. A sib of one of these children was microcephalic and retarded but radiographs of his skull were normal.

The reports of intracranial calcification associated with Pelizaeus-Merzbacher disease date from a period when the condition was poorly differentiated from Cockayne's syndrome. The case of Gerstl *et al*[10] probably had this latter condition although it was described as Pelizaeus-Merzbacher disease.

Patients with cerebro-oculo-facial-skeletal syndrome (COFS) may have intracranial calcification and some authors have suggested that this might represent an infantile form of Cockayne's syndrome.[11] However, the facial features of COFS (a prominent root to the nose, small eyes, large ear pinnae, cataracts, camptodactyly, flexion contractures, and rocker-bottom feet) were not present.

In conclusion, our patients clearly have the same syndrome of microcephaly, retardation, and intracranial calcification. Inheritance is either recessive or X linked, the latter on a simple frequency basis being less likely.

We would like to thank Dr Dick Hoare for reporting the CT scan, and the Department of Medical Illustration, The Hospital for Sick Children, Great Ormond Street, for help with the photographs.

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