Autosomal recessive severe congenital microcephaly: antenatal ultrasonographic diagnosis and head growth from 15 to 24 weeks of gestation

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SUMMARY A severely microcephalic, quadriplegic child without extracranial anomalies was born to a young non-consanguineous couple. Ultrasonographic examination at 15 weeks of the second pregnancy revealed a biparietal diameter that corresponded to 13 weeks, although the other measurements were in accordance with 15 weeks' gestation. Further examination at 20 and 24 weeks revealed progressive microcephaly. The aborted fetus (at 24 weeks' gestation) was grossly microcephalic, but lacked further abnormal findings. Antenatal ultrasonographic diagnosis of autosomal recessive microcephaly is feasible, at least in a proportion of cases.

Antenatal ultrasonographic diagnosis of autosomal recessively inherited congenital microcephaly without any other abnormalities has repeatedly been proposed as a measure to prevent the birth of a second affected child after the occurrence of the first (see, for example, Baraitser¹). To the best of our knowledge, antenatal diagnosis of primary microcephaly with autosomal recessive inheritance has been reported only once.² In this patient, head growth fell below the 3rd centile between the 18th and 22nd week of gestation, but the pregnancy was not terminated.

We report a family in which the first child had severe congenital microcephaly and in a second pregnancy microcephaly was detected by ultrasonographic determination of the biparietal diameter in the 15th week. Head growth was followed up until termination of the pregnancy at 24 weeks' gestation.

Case reports

PATIENT 1

The parents, both born in 1955, were referred for genetic counselling in 1981 after the birth of a grossly microcephalic female. Both parents were at least of average intelligence, the pedigrees were unremarkable, and consanguinity was very un-

likely. Gestation had been normal and there was neither exposure to a known teratogen nor an infection during pregnancy. From the 6th month onwards, the mother was repeatedly treated for premature contractions. Delivery, 4 days after term, was vertex after spontaneous onset of contractions. The patient weighed 2540 g, measured 44 cm in length, and had a head circumference of 26 cm; the placenta weighed 570 g. Apart from gross microcephaly, there was a mild mongoloid slant of the eyes, and the auricles were relatively large. Muscle tone was increased, but no other abnormalities were found on clinical examination. Computed tomography of the skull performed at 6 days of age revealed the following abnormalities: absence of an anterior fontanelle, several low density zones in the cerebellum and occipital lobes, the falx shifted to the right, no visible tentorium, enlargement and unusual shape of the third ventricle, lack of anterior segments of the lateral ventricles, posterior horns enlarged and extending laterally to the cisterna quadrigemina, and no dense gradient between grey and white matter of the cerebrum and cerebellum.

The child had to be tube fed for 12 months and from birth had severe neurological deficit and increasing spasticity causing flexion contractures, especially of the elbows, hips, knees, and ankles. The first smile was observed at about 4 weeks. Crying attacks started at 5 months of age, and the first grand mal seizure was observed at 8 months, subsequently requiring continuous antiepileptic

FIG 1 Patient 1 at 2 years 5 months of age.

medication. Bilateral hip dislocation developed at 6 months. Subsequent mental and motor development were profoundly delayed. At 2 years 5 months of age (fig 1) she is able to move her head from a lying position, but unable to roll over, sit, or move her tongue. She smiles, follows moving objects with her eyes, makes some attempt to grasp objects and can be spoon fed. Most of the time, she is happy when sitting in a baby chair. Length (75 cm), weight (7.4 kg), and occipitofrontal head circumference (33.4 cm) were -5.2 SD, -4.9 SD, and -8.4 SD, respectively. There were no signs of cataract or other ocular problems.

Banded chromosome studies revealed a normal karyotype, and investigation for antenatal infections was negative for cytomegalovirus, rubella, and toxoplasmosis. Therefore, the homozygous state of an autosomal recessive gene was considered the most likely cause of the severe primary microcephaly and mental retardation in this child. The parents were advised that there was a probable recurrence risk of 25% for any further child, and ultrasonic monitoring of cephalic growth in any further pregnancy was recommended, although it was admitted that no absolute guarantee could be given that microcephaly could be detected during the second trimester of the pregnancy.

PATIENT 2

The second pregnancy was confirmed on 1 March 1983 at 6 weeks 1 day of gestation. At that time, the size of the amniotic sac corresponded to the duration of the pregnancy. On 17 March, the amniotic sac measured 3.7 cm in diameter, corresponding to 9 weeks' gestation. Results of the following three measurements are given in fig 2. On 2 May, at 15 weeks' gestation, the biparietal diameter was 2.3 cm, normal for a gestation of 13 weeks, while

crown-rump length was 8.2 cm, corresponding to 15 weeks' gestation. The amount of amniotic fluid was normal for 15 weeks. On 2 June, at 20 weeks by dates, the biparietal diameter of 3.3 cm corresponded to 15 weeks, and on 27 June, at 24 weeks by dates, the biparietal diameter obtained by ultrasound was 4.0 cm (normal for 16 weeks' gestation). The amount of amniotic fluid was still normal for a 24 week gestation.

The pregnancy was terminated at 24 weeks' gestation by prostaglandin infusion. The female fetus (patient 2, fig 3) was grossly microcephalic, but appeared normal otherwise. Her measurements were: crown-heel length 28 cm (normal for gestational age: 38.6 ± 2.1 cm), weight 400 g (normal: 729 ± 17.6 g), occipitofrontal head circumference 17.3 cm (normal: about 23 cm), thoracic diameter 17.5 cm, abdominal diameter 14.5 cm.

Necropsy disclosed severe micrencephaly and hypoplasia of the brainstem. The brain weighed 12.7 g (normal: 112 g), the adrenals 1.34 g (normal: 3.2 ± 2.4 g), and placental weight was 130 g (normal for gestational age: 200 g). The remainder of the necropsy findings were normal.

FIG 2 Intrauterine head growth (biparietal diameters) of patient 2 from weeks 15 to 24 of gestation.

FIG 3 The 24 week old fetus (patient 2).

Discussion

According to Baraitser,¹ characteristic features of patients with autosomal recessive microcephaly include the following: receding forehead and chin, normal sized face, large auricles, only mild spasticity, normal early developmental milestones, few seizures, and a normal personality. Similarly, Qazi and Reed³ stated that in their series of cases with familial microcephaly with at least two affected sibs, quadriplegia was unusual and that 20 out of 26 patients walked and 14 out of 26 spoke. The IQs of 11 out of 24 parents tested were below average.⁴

These characteristics apparently apply to patients with much less severe microcephaly than was present in both sibs (and mental retardation in patient 1) of this report. Therefore, the question arises whether this discrepancy is due to different genes involved in our cases from those of 'common autosomal recessive microcephaly', different alleles, or one and the same mutant gene with variable expression. We do not at present have enough information on sibs with very different degrees of microcephaly and mental retardation to confirm or exclude the latter possibility. Vormittag *et al*⁵ reported three microcephalic sibs, of whom two were mentally retarded, and the third was profoundly retarded and bedridden; however, no further data, and particularly no head circumference measurements of the third sib, were presented.

Microcephaly of a similar degree to our patients was reported in two sibs by Lowry *et al*⁶ and in three sibs by Scott-Emuakpor *et al*.⁷ These five patients also had mental retardation, spasticity, and hip dysplasia similar to case 1 of the present report,

but they also had cataracts diagnosed between 3 weeks and 6 months in individual cases. Patients with the Neu-Laxova syndrome also have severe congenital microcephaly, pachygyria, and tetraplegia. However, these cases die early postnatally and show a pattern of characteristic further findings including ichthyosis, short digits, undermineralised bones, and partial syndactyly.^{8,9}

Antenatal ultrasonographic diagnosis of genetic microcephaly was recently reported by Pescia *et al*.² Because of the birth of a previous severely microcephalic child (OFC at birth 28 cm), several examinations were performed; the biparietal diameter was normal up to 18 weeks of gestation and fell below the 3rd centile between the 18th and 22nd week. The parents decided to continue the pregnancy, and therefore no further examinations were performed. At term, a male child with an OFC of 29.5 cm was born.

The present report demonstrates that the onset of severe microcephaly can be early enough in fetal development to allow for antenatal ultrasonographic detection early in the second trimester. In contrast to patient 2 of Pescia *et al*,² the biparietal diameter in our second sib was already distinctly below normal at 15 weeks' gestation, and microcephaly progressed during the period of observation up to week 24. Therefore, intrauterine onset of microcephaly was earlier in our family than in the family of Pescia *et al*.² The degree of microcephaly at birth was also more severe in the family of this report with an OFC at birth of 26 cm versus 28 and 29.5 cm respectively. Obviously, the ultrasonographic examinations in these two families do not allow one to conclude that every case of autosomal recessive microcephaly is detectable as early as the second trimester of pregnancy. As mentioned above, we do not know whether an affected sib, after the birth of a first affected child with a degree of microcephaly similar to our patient 1, will always, mostly, or only sometimes be similar with respect to the extent of microcephaly, neither do we know how early autosomal recessive microcephaly of milder degree (for example, even milder than in case 2 of Pescia *et al*²) is manifest in fetal life, and nor how frequently sibs of a more mildly affected patient will be mildly affected as well.

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References

- 1 Baraitser M. *The genetics of neurological disorders*. Oxford Monographs on Medical Genetics. Oxford, New York, Toronto: Oxford University Press, 1982: 21–2.

- ² Pescia G, Nguyen-The H, Deonna T. Prenatal diagnosis of genetic microcephaly. *Prenatal Diagnosis* 1983;3:363-5.
- ³ Qazi QH, Reed ET. A problem in diagnosis of primary versus secondary microcephaly. *Clin Genet* 1973;4:46-52.
- ⁴ Qazi QH, Reed ET. A possible major contribution to mental retardation in the general population by the gene for microcephaly. *Clin Genet* 1975;7:85-90.
- ⁵ Vormittag W, Kunze-Mühl E, Weninger M. Chromosomale Instabilität bei Homo und Heterozygotie für Microcephalia vera. *Humangenetik* 1975;26:307-14.
- ⁶ Lowry RB, MacLean R, MacLean D, Tischler B. Cataracts, microcephaly, kyphosis, and limited joint movement in two siblings: a new syndrome. *J Pediatr* 1971;79:282-4.
- ⁷ Scott-Emuakpor N, Heffelfinger J, Higgins JV. A syndrome of microcephaly and cataracts in four siblings. *Am J Dis Child* 1977;131:167-9.
- ⁸ Fitch N, Resch L, Rochon L. The Neu-Laxova syndrome: comments on syndrome identification. *Am J Med Genet* 1982;13:445-52.
- ⁹ Curry CJR. Letter to the Editor. Further comments on the Neu-Laxova syndrome. *Am J Med Genet* 1982;13:441-4.

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