
Case reports

Microcephaly-cardiomyopathy: a new autosomal recessive phenotype?

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Abstract

A distinctive phenotype of severe microcephaly and self-limiting dilated cardiomyopathy has been observed in two sibs suggesting autosomal recessive inheritance. Mental retardation, delayed developmental milestones, and minor dysmorphism were additional features.

Microcephaly is a common abnormality, both in isolation or as a component of genetic syndromes. While the majority of cases of microcephaly are non-genetic, a variety of anomalies may be inherited in association with microcephaly as autosomal recessive or X linked recessive traits.¹⁻⁵

There are many causes of dilated cardiomyopathy and familial forms are known to exist.⁵ In addition the disorder may form a component of various syndromes, such as familial cardiomyopathy with hypogonadism and collagenoma,⁶ and the Kearns-Sayre syndrome where ophthalmoplegia, cardiomyopathy, and pigmentary degeneration of the retina are features of a mitochondrial disorder.⁷

We have investigated two sibs with an apparently unique, clear cut phenotype comprising microcephaly, a dilated cardiomyopathy, and several minor dysmorphic features. Despite a computerised search

of published reports, we could find no previous documentation of this association.

Case reports

CASE 1

History

The patients were the only children of a healthy, young, unrelated couple of Afrikaner stock. No other family members were similarly affected.

The older sib, a male, was born in 1984 after a normal pregnancy. Although born at term, he was small for gestational age with a birth weight of 2340 g and an occipitofrontal head circumference 2 SD below normal. His neonatal period was uneventful. At the age of 2 months he developed cardiac failure and echocardiography confirmed the diagnosis of cardiomyopathy. Histological examination of endomyocardial tissue removed during cardiac catheterisation specifically excluded myocarditis. He was treated with digoxin and diuretics until the age of 3 years, at which time echocardiography confirmed that his cardiomyopathy had resolved. Treatment was discontinued and he has had no further cardiac problems. Subsequent echocardiographic studies have remained within normal limits.

In addition to the cardiac abnormalities, his developmental milestones have been retarded; he sat alone at 14 months and walked at the age of 3 years. Currently, at the age of 5 years 9 months, he has no speech and is not yet toilet trained.

Examination

Clinical examination was at 5 years 9 months of age, at which time striking microcephaly was evident (fig 1) (head circumference 45 cm). Other growth parameters were on the 3rd centile for his age. There was minimal facial dysmorphism, with cupping of the outer helix of both pinnae, bilateral fifth finger clinodactyly, and sandal gaps on both feet. The thorax was narrow but his cardiovascular status was

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Figure 1 The index patient in profile: microcephaly and dysmorphic ears are evident.

normal at this stage. Evaluation of the CNS showed normal tone and reflexes. Formal ophthalmological appraisal showed very fine pigmentary stippling at the posterior poles and macula of the fundus.

Baseline haematological and biochemical investigations were within normal limits, and a wide range of serological tests for viral and bacterial infection were negative. An ultrasonic scan of the head showed dilated lateral and third ventricles. BAER and audiometry were within normal limits. Cytogenetic investigation showed a normal male karyotype.

CASE 2

History

The sister of case 1, born in 1989, was delivered at term after an uneventful pregnancy. An ultrasonic scan, performed at approximately 30 weeks' gestation, indicated a small biparietal diameter. This investigation repeated at 32 weeks' gestation showed microcephaly with certainty and this was confirmed at birth. Her motor milestones were identical to those of her brother and, at the age of 5 months, she developed cardiac failure. Echocardiography confirmed a dilated cardiomyopathy and treatment with digoxin and diuretics was started.

Examination

The child's physical features were similar to those of her brother (fig 2). At the age of 12 months she had

an occipitofrontal head circumference 2 SD below normal (38 cm), a narrow thorax, reduced muscle tone, brisk reflexes, and she was unable to sit without support. In addition, she resembled her brother in that she had similar cupping of the pinnae, fifth finger clinodactyly, and sandal gaps on both feet. She had no ophthalmological abnormalities; examination under anaesthesia was not performed. As with her brother, none of the biochemical or radiographic investigations performed assisted in making a syndromic diagnosis.

Discussion

The coexistence of microcephaly, dilated cardiomyopathy, and similar minor dysmorphic features in two sibs would appear to be more than coincidence and we believe these manifestations represent an autonomous syndromic entity. The mild pigmentary changes in the ocular fundus of the boy were surprising; there was no ophthalmoplegia, ptosis, or deafness and neurological examination was unremarkable. The lack of these physical signs and the pedigree data make the diagnosis of Kearns-Sayre syndrome unlikely.

The pathogenesis of this syndrome is unknown; there were no exogenous factors during pregnancy or the perinatal period in either instance which might have caused the abnormalities. The occurrence of the condition in sibs of unlike sex with normal parents is compatible with autosomal recessive inheritance. The normal cytogenetic studies in the older child negate the possibility that the coexistence of these features was the result of a chromosomal deletion.

In terms of the long term prognosis, moderate or even severe mental retardation seems likely. However, the cardiac outcome seems more promising as the cardiomyopathy in the older child appears to have resolved and the younger child has markedly improved on anticardiac failure therapy.

Prenatal diagnosis by ultrasonic indication of microcephaly in future pregnancies may be possible. However, prenatal diagnosis of this feature in early pregnancy is difficult and there are few reports of microcephaly being detected before the third trimester.^{8,9} It is probable that the growth of the fetal head is within normal limits until the 28th week of gestation and thereafter the rate of growth reduces. This may explain the difficulty in the detection of microcephaly before the third trimester. This contention is supported in this family as the initial prenatal ultrasound scan performed on the second child at 30 weeks was equivocally small, but by 32 weeks the ultrasonologist was confident that the fetal head growth was reduced. In addition, the cardiac lesion only became evident several months after birth. For these reasons, the parents have been given



Figure 2 The similarity in facial features between the two sibs with microcephaly and cardiomyopathy is remarkable.

an empirical 25% recurrence risk for further pregnancies.

In summary, we have documented two children with microcephaly associated with severe mental retardation, delayed developmental milestones, mild dysmorphic facies, and onset of cardiomyopathy in infancy, which resolved spontaneously. This association of features appears to be unique and, in the absence of a teratogenic factor, is likely to be hereditary.

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