

## ELECTRONIC LETTER

## Microcephaly-cardiomyopathy syndrome: expansion of the phenotype

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In 1991, Winship *et al*<sup>1</sup> described South African sibs, one male child aged 5 years and one female child aged 12 months, with a combination of microcephaly, dilated cardiomyopathy, and minor dysmorphic features. The cardiomyopathy had resolved in the older child by the age of 3 years, and had markedly improved in the younger child on treatment for associated cardiac failure. The microcephaly was severe, and both children showed severe global developmental delay. The dysmorphic features were described as cupping of the outer helix of both pinnae, fifth finger clinodactyly, and sandal gaps on both feet. The older sib had fine pigmentary stippling at the posterior poles and macula of the fundus on ophthalmological examination.

Kennedy *et al*<sup>2</sup> reported on a 9 year old girl with microcephaly, severe developmental delay, and a dilated cardiomyopathy which had resolved at 7 years of age. She had had seizures in the immediate neonatal period, but not subsequently. This patient had a sloping forehead, downward slanting palpebral fissures, a narrow palate, small ears, and a big sandal gap. Magnetic resonance imaging of the brain was normal.

All three children initially presented with cardiac failure, at the ages of 2 months, 5 months, and neonatally respectively. There was no consanguinity in either family.

We describe another patient with microcephaly and a dilated cardiomyopathy, secondary hyperthyroidism, minor brain abnormalities, and cup shaped ears, but without any other soft dysmorphic features. No retinal changes or seizures occurred in our patient. Consanguinity in our family would support autosomal recessive inheritance.

## CASE REPORT

The male patient was the second child of first cousin parents originating from Pakistan; there were no concerns about his older sib, and there was no other relevant family history. He was born at 36 weeks by elective caesarean section for intrauterine growth retardation, reduced liquor volume, and absent end diastolic flow on umbilical Doppler analysis. A reduction of biparietal diameter was detected on antenatal

ultrasound at 29 weeks; the measurement corresponded to 24 weeks of gestation, indicating prenatal onset of microcephaly. His head circumference at birth was 27 cm (−4 SD), with a birth weight of 1510 g (just below the 0.4th centile). He did not require any resuscitation, there were no neonatal seizures, and he was discharged home after an uneventful 10 day admission to the neonatal unit.

At the age of 6 weeks, he presented in severe cardiac failure with a mixed respiratory and metabolic acidosis. He was admitted to a paediatric intensive care unit and was ventilated for five days. He also required inotropic support and diuretic drugs. Echocardiography showed a dilated heart with moderately severe mitral regurgitation and mild tricuspid regurgitation. The left atrial pressures were extremely high, and the overall picture was of a dilated cardiomyopathy with a restrictive component. His cardiac failure and overall condition improved, and he was discharged from hospital after six weeks on diuretic treatment. On cardiology review at 4 months of age, the echocardiogram still showed impaired left ventricular function with mild mitral and trivial tricuspid regurgitation. A repeat echocardiogram at the age of 7 months showed a moderately dilated left ventricle with improved contractile function and no evidence of mitral or tricuspid regurgitation. At 9 months, there was good biventricular function with normal atrial size.

Magnetic resonance imaging of the brain at the age of 3 months showed a small but structurally normal brain, a mild deficiency of the anterior septum pellucidum, and delayed myelination. His general development at 9 months was at the 8 month level. On examination at 10 months, he was more microcephalic with a head circumference of 36.4 cm (−6 SD). His weight was just below the 0.4th centile and his length was on the 2nd centile. He had cup shaped ears, but no other dysmorphic features were noted. In particular, he did not have fifth finger clinodactyly or a big sandal gap. He walked at 21 months and at 23 months had been referred to the speech therapist because of speech and language delay. At his most recent developmental assessment at 2 years of age, he had no recognisable words, but could understand simple commands. His hand skills were at the 21 month level and his performance skills at the 23 month level on the Griffith scales. His weight was just below the 0.4th centile, his height had increased to above the 25th centile, and he remained very microcephalic with a head circumference of 39 cm (−6 SD). Chromosome analysis showed a normal 46,XY karyotype, and the patient was not deleted for the 22q11 region as shown by fluorescence in situ hybridisation analysis. An extended metabolic screen was carried out which included plasma amino acids and urinary organic acids, lactate, very long chain fatty acids and plasmalogens, transferrin electrophoresis, cholesterol, triglycerides, vacuolated lymphocytes, and a carnitine profile. No abnormalities were found apart from hypothyroidism, requiring thyroxine treatment. The initial thyroid function test showed a free T4 concentration of <2.5 pmol/l and a TSH concentration of 0.3 mU/l. This suggests secondary hypothyroidism of pituitary or hypothalamic

## Key points

- Three children, two sibs and one single case, have previously been reported with a combination of microcephaly, a self-limiting dilated cardiomyopathy, severe developmental delay, and dysmorphic features.
- We describe another patient with microcephaly, a resolving dilated cardiomyopathy, developmental delay, secondary hypothyroidism, minor brain abnormalities, and cup shaped ears.
- This child was born to first cousin parents originating from Pakistan. Consanguinity in our family would support autosomal recessive inheritance.

origin. Subsequent thyroid function tests on thyroxine have been within the normal range. Further endocrine tests to investigate the nature of the hypothyroidism are planned. Cortisol, LH, FSH, and prolactin concentrations were normal, and a test for antinuclear antibody was negative. An ophthalmological examination suggested a minor degree of astigmatism; there were no retinal abnormalities. The serology results for cytomegalovirus, rubella, and toxoplasma were negative.

## DISCUSSION

Cardiomyopathies can have a genetic basis, but can also occur with viral infections, as a side effect of drug treatment, with cardiac arrhythmias, because of an immunological abnormality, or because of exposure to various environmental toxins. The combination of microcephaly and a cardiomyopathy is more unusual. We found no evidence of a metabolic cause in our patient, such as a disorder of amino acid, fat, or carbohydrate metabolism, a storage disorder, or mitochondrial disease. There was no maternal diabetes, and a limited viral screen was negative. Telomere screening was not pursued in the absence of other dysmorphic features. The clinical features fit well into the microcephaly-cardiomyopathy syndrome range. Because of the lack of additional clinical features, other possible syndrome associations such as Alstrom syndrome are much less likely. In Alstrom syndrome, there are usually visual problems soon after birth, and microcephaly would be unusual, although a reversible cardiomyopathy can occur.<sup>3</sup> We think that this is the third report of a patient with the microcephaly-cardiomyopathy syndrome, the first patient of Pakistani descent. The first report in a male and female sib pair by Winship *et al*<sup>1</sup> suggested autosomal recessive inheritance, and the fact that our patient was born to consanguineous parents would support this. The cardiac presentation in all four cases was one of cardiac failure and a dilated cardiomyopathy which improved with time and was self limiting in the two older children. The microcephaly, however, was severe in all cases. In our case, the microcephaly was already present antenatally from about 29 weeks. In the second sib reported by Winship *et al*,<sup>1</sup> ultrasound scans in the pregnancy showed a small biparietal diameter at 30 weeks, and definite microcephaly at 32

weeks; in the other two patients, antenatal ultrasounds were not specifically mentioned. Developmental assessments in our patient so far suggest that the outcome may be better than in the previously reported cases. He is the first patient with documented minor brain abnormalities, but brain imaging was not carried out in the two sibs from the initial report. The dysmorphic features in all four reported patients are soft and not consistent, which could be explained by phenotypic variation, or they may represent familial traits. Our patient has cup shaped pinnae similar to the sibs reported by Winship *et al*,<sup>1</sup> but the patient reported by Kennedy *et al*.<sup>2</sup> did not have this feature. The secondary hypothyroidism in our patient has not been reported before, and it is not clear whether this is part of the phenotypic range. The complete resolution of the dilated cardiomyopathy which forms part of this condition is unusual and will need further investigation.

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