

Microcephaly-cardiomyopathy syndrome: confirmation of the phenotype

Shelley J Kennedy, Kyong-Jin Lee, Brian W McCrindle, Ahmad S Teebi

Abstract

We report a 9 year old girl with microcephaly and self-limiting dilated cardiomyopathy. Additional features include mental retardation, delayed developmental milestones, and minor dysmorphic features. This is the second reported case of this phenotype, which is believed to be a new autosomal recessive syndrome.

(*J Med Genet* 1999;36:854-855)

Keywords: microcephaly-cardiomyopathy syndrome; mental retardation

Microcephaly is defined as a head circumference that is at least 3 SD below the mean for age and sex. It is a highly heterogeneous condition that can be the result of a variety of genetic and environmental factors, which affect brain growth both prenatally and postnatally. Microcephaly can be seen in isolation or as a feature of a genetic syndrome. The incidence of genetic microcephaly is estimated to be between 1 in 25 000 and 1 in 250 000 live births.^{1,2} Cardiomyopathy is defined as a disease of the myocardium characterised by the presence of systolic or diastolic dysfunction or abnormal myocardial structure.³ Cardiomyopathy, like microcephaly, can have diverse aetiologies ranging from maternally transmitted viral infections to mendelian syndromes.⁴ Cardiomyopathy is uncommon in malformation syndromes and when it presents with major or minor anomalies, a recognisable syndrome is often not identifiable.⁵

In 1991, Winship *et al*⁶ reported a brother and sister with a distinctive phenotype of severe microcephaly and self-limiting cardiomyopathy. They suggested that this clinical presentation, which also included mental retardation, delayed developmental milestones, and minor dysmorphic features, represented a new autosomal recessive phenotype. Recently, we evaluated a 9 year old female who, we believe, has the same condition. The purpose of this report is to delineate further the clinical spectrum of this disorder.

Case report

The patient was born to a 26 year old primigravida and her healthy, non-consanguineous husband. A review of the fam-

ily history was unremarkable. There were no cases of birth defects or mental retardation. The pregnancy was normal apart from slight spotting at 10 weeks' gestation. There were no exposures to recognised human teratogens. The patient was delivered at term by spontaneous vaginal delivery without complication and had a birth weight of 3050 g (25th centile). The head circumference was 35 cm at 5 weeks of age (3rd centile). The immediate neonatal course was complicated by seizures and congestive heart failure with cardiomegaly associated with a midmuscular ventricular septal defect (VSD). Investigations at this time included a CT scan of the brain, an EEG, and chromosome analysis, results of which were normal.

The patient's early developmental milestones were delayed. At 10 months, she had not yet crawled nor was she pulling to stand. Speech development was also delayed and at 10 months she had not said "mama" or "dada". The patient did not walk or obtain a pincer grasp until 3 years of age, showing delay in both gross and fine motor skills.

The cardiac course of this patient evolved as follows. At 3 months of age the patient was asymptomatic on digoxin and aldactazide and was noted to have a harsh blowing grade III/VI pansystolic murmur. A chest x ray at this time was unusual in that it showed persistent cardiomegaly in spite of the evidence that the VSD was becoming restrictive. On echocardiography, ventricular function was normal with an ejection fraction of 59%. Cardiac structure was normal with the exception of a small restrictive VSD. At 6 months of age, on echocardiography the VSD was restrictive with a gradient of 76 mm Hg, an ejection fraction of 58%, with some left ventricular dilatation indicated by a left ventricular end diastolic dimension of 3 cm. At 3 years of age the assessment was that the patient had dilated cardiomyopathy of unknown aetiology. An echocardiogram showed that the VSD was almost closed in appearance and with increased Doppler gradient. It was noted that some areas of the left ventricle had the appearance of persistent fetal trabeculations. The ejection fraction was 47%, decreased from one year previously (62%). The ventricular dysfunction could not be attributed to the haemodynamically insig-

Division of Clinical Genetics, Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X5, Canada
S J Kennedy
A S Teebi

Division of Cardiology, Hospital for Sick Children, Toronto, Ontario, Canada
K-J Lee
B W McCrindle

Correspondence to:
Dr Teebi.

Revised version received
13 May 1999
Accepted for publication
7 July 1999

Table 1 Manifestations of microcephaly-cardiomyopathy syndrome

Feature	Present case	Winship <i>et al</i> ⁶		Total
		Case 1	Case 2	
Sex	Female	Male	Female	
Developmental delay	+	+	+	3/3
Microcephaly	+	+	+	3/3
Cardiac failure	+	+	+	3/3
Dilated cardiomyopathy	+	+	+	3/3
Resolution of cardiomyopathy	+	+	-	2/3
Cupping of pinnae	-	+	+	2/3
5th finger clinodactyly	-	+	+	2/3
Sandal gap	+	+	+	3/3
Ophthalmological abnormality	-	+	-	1/3

- = absent, + = present.

nificant VSD. Digoxin, which had been stopped the previous year because the VSD was felt to be haemodynamically insignificant and there were no signs of congestive heart failure, was restarted. By 5 years of age, the patient's VSD had spontaneously closed and there was no audible murmur. The ejection fraction was 53%. At 7 years of age, an echocardiogram showed complete resolution of diminished ventricular function with no evidence of hypertrophy. The ejection fraction was normal at 65%. At 9 years of age, there were no structural or functional abnormalities related to past cardiomyopathy detected on echocardiogram, and digoxin was discontinued.

The patient was recently assessed at the genetics clinic at 9 years of age. Her head circumference was 48 cm (<3rd centile or the 50th centile of a 2 year old female), weight was 29 kg (50th centile), and height was 125 cm (25th centile). Craniofacial manifestations included a sloping, short forehead with slightly downward slanting palpebral fissures. She has a narrow palate and overcrowded teeth. Her ears are relatively small. Her hands appeared normal and the feet showed long halluces with a gap between the first and second toe. No heart murmurs were heard and the chest examination was normal. The gait was unsteady, but no intention tremors or focal abnormality was present. She has poor expressive language skills and mainly communicates with sign language and picture symbols. She is currently in grade 4 with the assistance of a special educator. Her parents report that her

receptive language skills are good. Behavioural problems include an inability to sleep through the night and obsessive picking of skin sores.

Investigations and medical procedures that have been performed include an auditory evoked brain stem response, which showed 25% hearing loss. Testing for maternal PKU and congenital CMV was negative. High resolution banding to examine regions 15q11-13 and 22q11 and fluorescence in situ hybridisation for 17q11.2 (Smith-Magenis syndrome) were negative. Magnetic resonance imaging of the brain was normal. Surgery for bilateral exotropia was performed at 1.5 years of age. At the age of 9, a visual evoked potential was performed and was normal, with responses from the right eye being consistent with amblyopia. There were no other ophthalmological abnormalities.

Discussion

The features in this patient are similar to those of the sibs in the report of Winship *et al*⁶ (table 1). All patients have the same presentation, consisting of microcephaly, developmental delay, and spontaneously resolving dilated cardiomyopathy in addition to some minor dysmorphic features. Because of the small number of cases known so far, it is not clear if some of the minor anomalies noted in the first report are part of the syndrome or coincidental familial traits. Additional cases need to be reported to discover the spectrum of anomalies associated with this new microcephaly-cardiomyopathy syndrome.

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