An unusual presentation of cardiomyopathy in a patient with microcephaly-cardiomyopathy syndrome

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We report the case of a 15-year-old male patient with microcephaly, dilated cardiomyopathy, mental retardation, secondary hypopituitarism, and minor dysmorphic features: downward- slanting palpebral fissures, narrow palate, small and low-set ears, fifth finger clinodactyly, sandal gaps on both feet, and anal stenosis. He was admitted to the pediatric intensive care unit with signs of progressive cardiac failure. Lethal outcome occurred 25 days after admission. Most clinical features of the patient were similar to those of the four previously reported patients with microcephaly-dilated cardiomyopathy syndrome, but some of this patient's features, such as anal stenosis and secondary hypopituitarism, were unique.

Key words: microcephaly-cardiomyopathy syndrome, mental retardation.

Microcephaly is defined as a head circumference that measures more than three standard deviations below the mean for age and sex. The main characteristic of dilated cardiomyopathy is reduced left ventricle systolic function with increased left ventricle end-diastolic diameter.

In 1991, Winship et al.[1] described severe microcephaly with mental retardation and resolving dilated cardiomyopathy in a male and female sib pair. The authors suggested autosomal recessive inheritance. Only two cases have been reported since then[2,3]. The third reported patient was the first one with documented minor brain abnormalities and secondary hypothyroidism[3].

We present probably the first case of a male adolescent with two new anomalies associated with microcephaly-dilated cardiomyopathy syndrome: anal stenosis and hypopituitarism.

The aim of this report is to give further details about the spectrum of clinical features associated with this syndrome, and to describe the unusual clinical course and outcome of cardiomyopathy in a patient with microcephaly-cardiomyopathy syndrome.

Case Report

The male patient we report was the first child of nonconsanguineous Serbian parents. There were no concerns about his younger sib, and there was no other relevant family history. There were no exposures to recognized human teratogens. He was delivered at the 38th week of gestation by spontaneous vaginal delivery without complications. His birth weight was 2500 g (5th percentile for 38th gestational week). The head circumference was 32 cm (< 3rd percentile) and birth length 48 cm (P_{10} - 25th percentile). Anal stenosis was noticed after delivery for which the infant was operated at the age of 15 months. The neonatal and preschool periods were complicated by frequent diarrhea. The patient's early developmental milestones were delayed. He enrolled in school at the age of 8 (normal: between 6-7 years of age). At the most recent developmental assessment at the age of 15 years, he had IQ_{total} 61 (IQ_{verbal} 59; IQ_{motor} 62), which was characterized as mild mental retardation. At the age of 7 years, hypopituitarism was diagnosed, requiring growth hormone treatment.

Recently, he presented with nausea, emesis,

weakness, dark-colored urine and jaundice, and was admitted at the regional clinical center. The patient developed clinical signs and symptoms of congestive heart failure and was transferred to the tertiary institution – the pediatric intensive care unit of the Mother and Child Health Care Institute of Serbia, Belgrade.

On admission, the height of this 15 years and one-month-old boy was 148 cm (10 cm below 5th percentile), his weight was 40 kg (3 kg below 5th percentile), and his head circumference was 48.5 cm (below 3rd percentile; 5th percentile for the age of 3 year). He used eyeglasses: -8D (right), -11D (left). Craniofacial features included downward-slanting palpebral fissures and narrow palate. His ears were relatively small and low (Fig. 1). Fifth finger clinodactyly and sandal gaps on both feet were present.

Laboratory examination included bilirubin, cholesterol, triglyceride, aminotransferases (aspartate [AST], alanine [ALT]), creatine phosphokinase (CPK), muscle fraction of CPK, lactate, lactate-dehydrogenase, alkaline phosphatase, and C-reactive protein. No abnormalities were found. Troponins were normal. He had no hypoglycemia or metabolic acidosis during this or earlier hospitalizations. Sedimentation rate was normal. Metabolic screening of urine was normal. Chromosomal analysis showed a normal male - 46,XY karyotype. There was no microdeletion of 22q11. Urea and creatinine serum levels were elevated until the third day of hospitalization, whereas serum acid uric level was elevated during the whole period of hospitalization. Presence of neutralizing antibody titer to a Coxsackie virus B_1-B_5 was registered. Serum concentrations of IgG, IgA and IgM were normal. Echocardiogram showed severe dilated cardiomyopathy with poor contractility of the left ventricle and ejection fraction of 15%. Chest X-ray confirmed cardiomegaly with normal pulmonary vascularity. The presence of supraventricular extrasystoles, occasionally in pairs, was confirmed by 24-hour Holter ECG monitoring. Left bundle branch block was also noticed. On day 15 of the hospitalization, he became febrile with general weakness, chest pain, cough, and diarrhea. Series of blood and stool cultures were negative. His condition deteriorated and mechanical ventilation was started, but without improvement. Although the complete

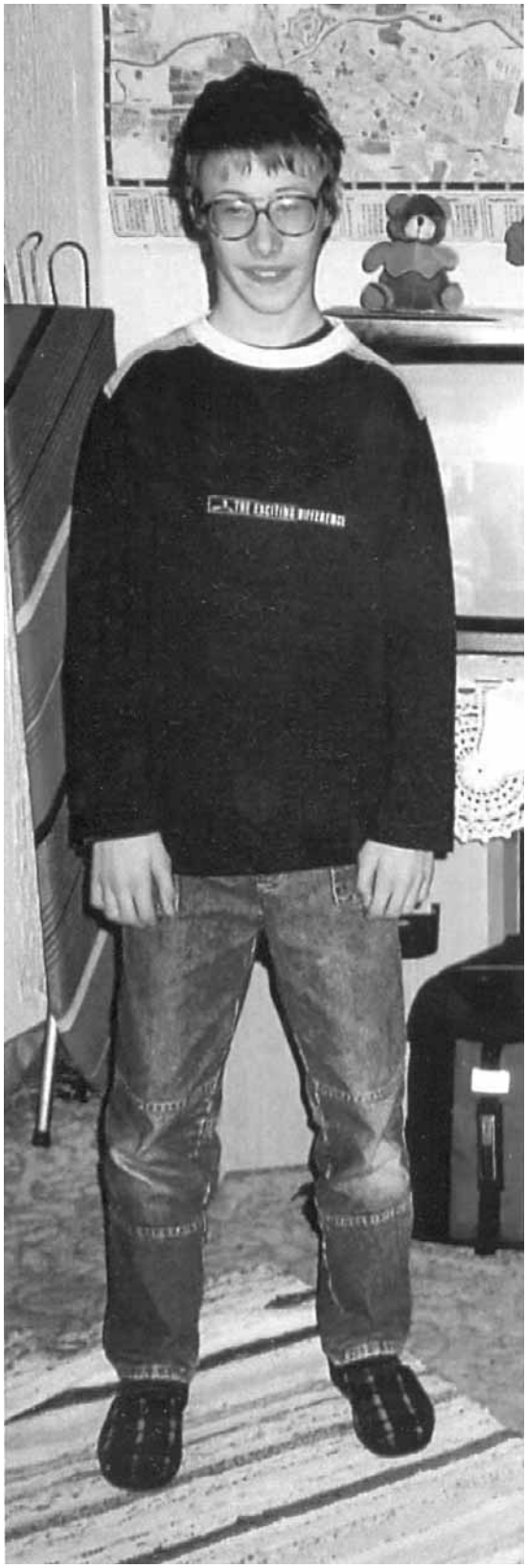

Fig. 1. Photograph of the patient with microcephaly-cardiomyopathy syndrome.

reanimation procedure was undertaken, the outcome was fatal. The parents did not accept clinical autopsy.

Discussion

We present a patient with microcephaly, dilated cardiomyopathy, anal stenosis, secondary hypopituitarism, downward-slanting palpebral fissures, narrow palate, small and low-set ears, fifth finger clinodactyly, and sandal gaps on both feet. Table I presents the characteristics of the previously described patients and our patient.

In 1999, Kennedy et al.[2] described one female child aged nine with microcephaly, severe developmental delay and resolving dilated cardiomyopathy. The immediate neonatal period was complicated by seizures, but not subsequently. This patient had sloping forehead, downward-slanting palpebral fissures, narrow palate, small ears, and big sandal gap. Magnetic resonance imaging of the brain was normal.

Becker and Yates[3] reported another patient with microcephaly, resolving dilated cardiomyopathy, developmental delay, secondary hypothyroidism, minor brain abnormalities, and cup-shaped ears, but without any other soft dysmorphic features. No retinal changes or seizures occurred in their patient. The child was the second child of first-cousin parents originating from Pakistan. Consanguinity in his family supported autosomal recessive inheritance. In the patient described in this report, extended investigation did not find any evidence of metabolic, immunological or viral cause of the disease. Normal levels of lactate and glycemia in several measurements excluded glycogen storage disease and respiratory chain disorders. The metabolic screening of urine excluded mucopolysaccharidoses. Friedreich ataxia and Steinert disease have specific neurological manifestations not observed in our patient. Fatty acid oxidation disorders present with hypotonia, hypoglycemia, signs of hepatic failure, and hypertrophic cardiomyopathy, and do not present with combination of dilated cardiomyopathy and microcephaly. Our patient had no sensorineural hearing loss, seizures, or hirsutism characteristic for the 1p36 deletion[4].

All four children initially presented with cardiac failure at the age of two months, five months, neonatal, and six weeks, respectively. Cardiac failure and dilated cardiomyopathy in the first four cases improved with time and was self-limiting in the two older children. Contrary to these reports, signs and symptoms of heart failure in our patient appeared at the age of 15 years and did not improve with time. On the other hand, microcephaly was uniformly severe in all reported cases.

Anal stenosis and the secondary hypopituitarism observed in our patient have not been reported before. It is not clear whether or not they are parts of the phenotypic range. The dysmorphic features in all the reported patients were soft

Table I. Clinical Manifestations of the Present and Previously Described Cases

Authors	Winship[1]		Kennedy[2]	Becker[3]	Kuburović	Total
Patient	1.	2.	3.	4.	5.	5
Sex	M	F	F	M	M	3:2
Growth retardation	+	+	+	+	+	5/5
Microcephaly	+	+	+	+	+	5/5
Cardiac failure	+	+	+	+	+	5/5
Dilated cardiomyopathy	+	+	+	+	+	5/5
Resolved cardiomyopathy	+	-	+	+	-	3/5
Malformed ear	+	+	-	+	+	4/5
Clinodactyly of 5th finger	+	+	-	-	+	3/5
Sandal gap	+	+	+	-	+	4/5
Ophthalmologic abnormalities	+	-	-	-	+	2/5
Endocrinologic abnormalities	-	-	-	+	+	2/5

and inconsistent, which could be explained by phenotypic variation, or may represent familial traits. The lethal outcome in our patient with nonresolving dilated cardiomyopathy is unusual. The fact that the dilated cardiomyopathy did not resolve in our case, in contrast with the previously reported cases, might be explained by its late presentation. Fatal outcome of dilated cardiomyopathy in a 15-year-old boy may well be the natural course of the disease. Literature data show that younger age at onset has been reported to be associated with better survival. One year survival has been reported to be 70%, decreasing to 65% by five years and to nearly 50% beyond 10 years[5].

Further investigation and more reported cases are obviously necessary to clarify these issues.

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