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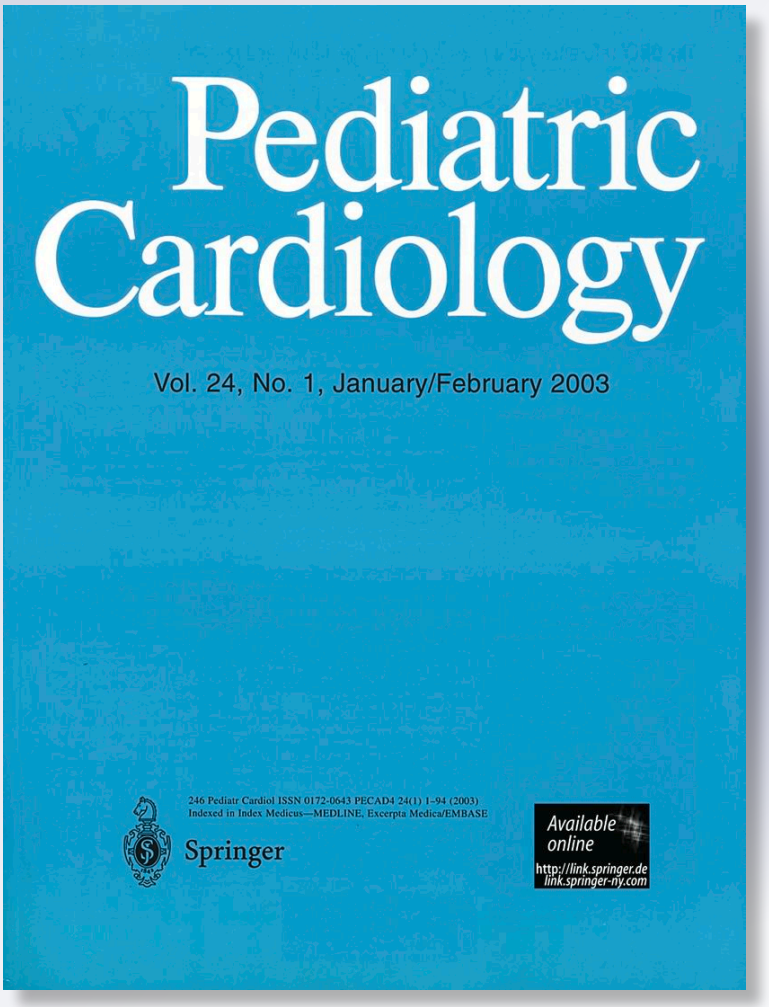

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CASE REPORT

Extreme Clinical Variability of Dilated Cardiomyopathy in Two Siblings With Alström Syndrome

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Abstract Alström syndrome (ALMS) is a rare autosomal recessive disorder caused by mutations in the *ALMS1* gene. We report two brothers, 3 and 4 years of age and diagnosed with ALMS, who initially presented in infancy with severe dilated cardiomyopathy during febrile respiratory infection. The disease course in the two siblings was marked by significant intrafamilial variability. Although cardiomyopathy in the older sibling has mainly resolved thus allowing for the discontinuation of medical therapy, heart function in the younger sibling continues to deteriorate despite maximal drug support with furosemide, carvedilol, captopril, and aldospirone. Genetic analysis revealed homozygous mutations, c.8008C>T (R2670X), in ALMS1 resulting in premature protein truncation. This report further emphasizes the exceptional intrafamilial variability of ALMS, mainly during the natural course of cardiac disease.

Jamal Mahamid and Avraham Lorber contributed equally to this study.

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Keywords Alström syndrome · Dilated cardiomyopathy · Autosomal recessive · *ALMS1* gene

Introduction

Alström syndrome (ALMS) is a rare monogenic disease caused by recessively -inherited mutations in the *ALMS1* gene [2]. The disease is characterized by multisystemic involvement, including progressive cone-rod dystrophy eventually leading to complete blindness; sensorineural hearing loss; childhood obesity; multiple endocrine dysfunction, including type 2 diabetes mellitus; pulmonary disease; and variable involvement of other systems [10]. Dilated cardiomyopathy (DCM) is one of the major manifestations of ALMS and ranges from sudden-onset infantile congestive heart failure (CHF) and DCM, which often resolves with treatment, to adult-onset cardiomyopathy, sometimes of the restrictive hypertrophic form, and CHF; often with a poor prognosis. Of note, approximately one third of ALMS patients will never develop cardiac involvement. CHF in infancy or early childhood, along with nystagmus and photophobia, are strong evidence leading to the correct diagnosis of ALMS. Importantly, infantile CHF can recur in adolescence or adulthood with a poor prognosis for affected patients [10]. Here we present two brothers with ALMS with completely different courses of cardiac disease.

Case Reports

The patients are two brothers born to healthy parents of Arab Muslim origin.

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Case No. 1

This 4-year-old boy was born at term after an uncomplicated pregnancy and vaginal delivery. His birth weight was 2,900 g. He was first admitted at 4 weeks of age with cyanotic spells and severe respiratory distress. Echocardiography showed dilated left atrium and left ventricle with 26 % shortening fraction (normal range 30–40 %) and mild tricuspid regurgitation resulting in a diagnosis of DCM. Medical treatment, including furosemide, digoxin, and angiotensen-converting enzyme inhibitors, was started. Surprisingly, on follow-up, steady improvement of his cardiac function was observed, allowing gradual decrease of his medical treatment until complete resolution was achieved.

Photophobia, nystagmus, and visual disturbance developed gradually during the patient's second year of life with concomitant deterioration of visual acuity. At age 3 years, electroretinogram (ERG) and visual evoked potential (VEP) studies revealed severe bilateral cone-rod dystrophy.

Beginning at age 2 years, the patient's weight increased gradually and crossed weight centiles from the 50th centile to 4 SD above the mean. This weight gain was not associated with appropriate height gain as reflected by his body-mass index of 23.5 (3.5 SD above the mean) at age 3 years. His laboratory chemistries were unremarkable except for mild to moderate hypertriglyceridemia and hypercholesterolemia. Glucose levels, as well as liver and renal function, were normal. In addition, he displayed mild to moderate motor delay, although no deficits were found on neurological examination. He attends a mainstream educational system but receives physical and occupational therapy. His last cardiologic and echocardiographic examination at age 4 years, with shortening fraction of 35 %, was normal (Fig. 1b).

Case No. 2

This 3-year-old patient is the younger brother of case no. 1. He was born spontaneously at 35 weeks' gestation by vaginal delivery, after an unremarkable pregnancy, and had a birth weight of 2,750 g (10th centile).

This patient first presented at 4 months of age with severe respiratory distress. His disease course was complicated by evolving CHF requiring admission to the pediatric intensive care unit due to severe dilation of the left ventricle with systolic shortening fraction of 10 %. The patient was given mechanical ventilation and aggressive treatment with furosemide, digoxin, aldacton, and captopril. Subsequently, he has had several episodes of febrile illnesses and pneumonia, with severe decrease of his cardiac function, which required admission to the PICU and titrating of his heart medications.

Similar to his older brother, this patient's photophobia and nystagmus evolved gradually toward the end of the first year of life. Initially, ophthalmologic evaluation disclosed hypermetropia, but otherwise his examination, in particular the optic discs, was normal. ERG and VEP studies at age 2.5 years were compatible with severe cone-rod dystrophy. Laboratory assessment, including serum glucose and lipid profile as well as liver and renal function, was unremarkable. He also displayed generalized developmental delay, mainly fine and gross motor function, which was partly attributed to his cardiac dysfunction disrupting his well being and to the recurrent admissions during febrile illnesses.

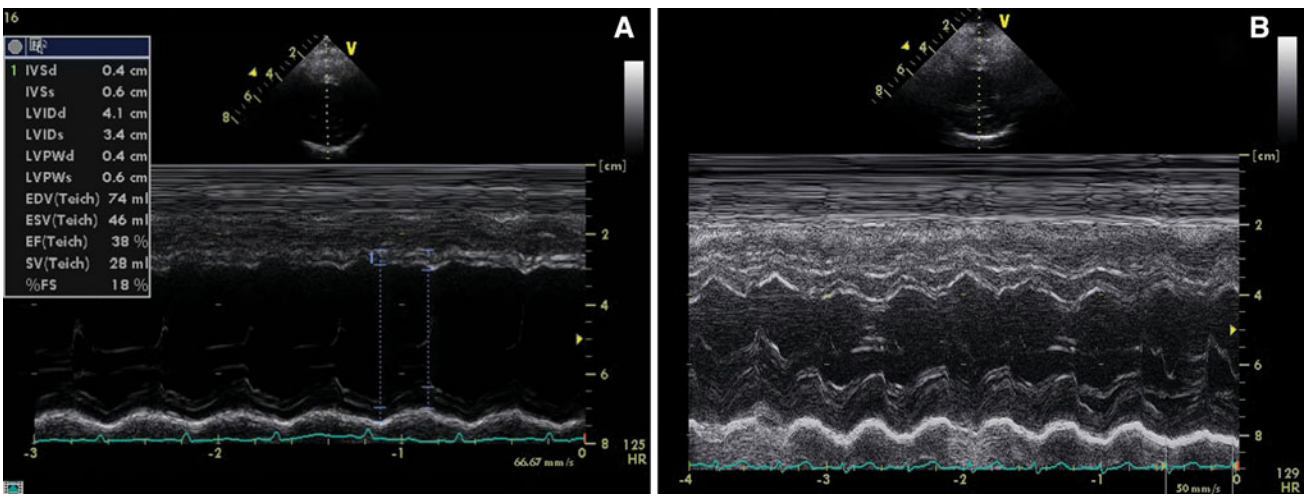

Fig. 1 Two-dimensional guided left-ventricular M-mode echocardiography shows normal left-ventricular function and left-ventricular fractional shortening of 35 % in case no. 1 at age 4 years (**b**) and dilated left ventricle and decreased left-ventricular function with fractional shortening of 18 % in case no. 2 at age 3 years (**a**). *S* systole, *D* diastole, *LV* left ventricle, *RV* right ventricle, *LVPW* left ventricle posterior wall, *IVS* inter-ventricular septum and *FS* fractional shortening

At present, at age 3 years, this patient's weight is 10 kg (3 SD below the mean). He is currently being treated with the combination of furosemide, carvedilol, aldospirone, and captopril. His most recent cardiologic examination showed left apical deviation with an apical systolic murmur, and echocardiography revealed dilated left ventricle with marked global decrease of systolic function and fractional shortening of 18 % (Fig. 1a).

Microarray and sequence analysis of the *ALMS1* gene identified both siblings to be homozygous for a nonsense mutation in exon 10 of ALMS1, c.8008C>T, which is predicted to result in early truncation of the ALMS1 protein (p.R2637X) [12]. Both parents were carriers for the mutation. This mutation has been previously reported in other patients with ALMS [1, 11].

Discussion

DCM is a myocardial disorder characterized by a dilated left ventricle and systolic dysfunction that commonly results in CHF. There are various causes of DCM, the most common of which is myocarditis. Other causes can include neuromuscular disorders, familial isolated DCM (inherited as either autosomal recessive, autosomal dominant, or x-linked), inborn errors of metabolism, and multisystemic genetic syndromes [13]. Therefore, the identification of the underlying cause of an isolated case of DCM is a major challenge both for the general pediatrician and the pediatric cardiologist. This task may be simplified by the co-occurrence of other affected systems, which may indicate a specific genetic syndrome and/or the existence of similar affected family members, suggesting a presumable mode of inheritance. The two siblings presented initially with CHF in infancy due to severe DCM. At that time, an autosomal recessive disorder was predicted, but the lack of other progressive manifestations failed to deliver a specific diagnosis. Only later, when retinal dystrophy was identified, did the combination of infantile DCM and early onset cone-rod retinal degeneration strongly suggest ALMS, which was further confirmed by the identification of homozygous *ALMS1* gene mutations in both siblings.

The complete resolution of DCM in the older sibling is of major significance. This is even more striking when compared with the severe cardiac disease progression in the younger sibling. Spontaneous resolution of myocardial function has been reported in a subset of pediatric myocarditis patients [3]. Although the early descriptions of ALMS failed to include cardiomyopathy as a frequent feature, the common prevalence of DCM in ALMS during infancy (almost 50 %) has been increasingly recognized in the past few decades [9, 10]. Surprisingly, of those who survive, most will make an apparently full or near complete recovery [1, 9]. Therefore, resolving cardiomyopathy, especially when combined with ophthalmologic abnormalities, such as photophobia, nystagmus, or retinal changes, should alert the physician to pursue ALMS1 genetic analysis.

The intrafamilial variability of cardiac presentation between the two siblings is a remarkable finding. A similar variability was previously shown by Hoffman et al. [6] who reported four siblings with ALMS. Three siblings presented with infantile DCM: Two of them resolved completely, and one displayed near full recovery but later experienced some deterioration in cardiac function. The fourth sibling experienced the most severe course, culminating in end-stage heart failure after unsuccessful heart transplantation. Our report further emphasizes this familial variability both in the course and prognosis of cardiac disease. The clinical variability may be in part due to modifying alleles of genes that interact with ALMS to alter the onset and course of cardiac disease in ALMS.

The localization of the *ALMS1* gene to the centrosomes and basal bodies, the structure from which the primary cilium arises [5], implicates ALMS1 in ciliogenesis and/or normal ciliary function as well as intracellular trafficking and protein transport, and places ALMS among the growing list of ciliopathies [4]. Despite the putative role of ALMS1 in ciliary function, the pathophysiology of cardiomyopathy in ALMS is not understood. Although echocardiographic studies performed in a cohort of ALMS patients demonstrated DCM [8], recent autopsy and cardiac MRI studies confirmed that the pathogenic process is mainly the result of myocardial fibrosis [7, 9]. A recent study performed on ALMS1-deficient fibroblasts support these findings by showing an increased tendency for tissue fibrosis [14]. Most cases of myocardial fibrosis are gradual and nonreversible; thus, the infantile onset of DCM and the high rate of resolution are difficult to explain. We thereby speculate that another pathogenic process may underly the infantile onset of cardiac ALMS. At early stages of infancy, the DCM may be reversible, but as the patient becomes older and significant myocardial fibrosis occurs, it becomes irreversible, and the prognosis is poor. Future studies are needed to clarify the evolution of myocardial disease and its heterogeneous course in ALMS patients.

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