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## Pediatric Myocarditis: a sentinel of non-cardiac chronic diseases?

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| **Abstract:** | Background: Although long term outcome studies in large pediatric myocarditis/cardiomyopathy populations have been reported in literature, none of them focused on comorbidities. Methods: All children and adolescents (age <18 years) treated with myocarditis at the Department of Pediatrics, University of Debrecen, Hungary were followed. Patients suffering from myocarditis during the period 1996-2011 were enrolled. Results: Over the 16-year period, a diagnosis of myocarditis was established in nine children. Their median age was 1.11 (0.03-8.71) years. Three of the nine patients died. Left ventricular dilatation and ejection fraction normalized within 1-21 months in the survivors. None of the cases progressed to dilated cardiomyopathy. Regarding non-cardiac comorbidities, myocarditis or recurrent peri-myocarditis preceded the manifestation of celiac disease in two patients, while cystic fibrosis was diagnosed after the improvement of cardiac function in another, and Alström syndrome was diagnosed several years after complete recovery from myocarditis in yet another patient. Conclusion: These results suggest that manifestations of other chronic pediatric diseases may be more frequent among survivors of pediatric myocarditis. Prolonged follow-up of patients who survive myocarditis is therefore recommended not only to detect possible progression to cardiomyopathy, but also to identify non-cardiac comorbidities. |
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# Pediatric Myocarditis: a sentinel of non-cardiac chronic diseases?

## *Running title: Non-cardiac comorbidities in pediatric myocarditis*

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**Abstract**

*Background:* Although long term outcome studies in large pediatric myocarditis/cardiomyopathy populations have been reported in literature, none of them focused on comorbidities. *Methods:* All children and adolescents (age <18 years) treated with myocarditis at the Department of Pediatrics, University of Debrecen, Hungary were followed. Patients suffering from myocarditis during the period 1996–2011 were enrolled. *Results:* Over the 16-year period, a diagnosis of myocarditis was established in nine children. Their median age was 1.11 (0.03–8.71) years. Three of the nine patients died. Left ventricular dilatation and ejection fraction normalized within 1–21 months in the survivors. None of the cases progressed to dilated cardiomyopathy. Regarding non-cardiac comorbidities, myocarditis or recurrent peri-myocarditis preceded the manifestation of celiac disease in two patients, while cystic fibrosis was diagnosed after the improvement of cardiac function in another, and Alström syndrome was diagnosed several years after complete recovery from myocarditis in yet another patient. *Conclusion:* These results suggest that manifestations of other chronic pediatric diseases may be more frequent among survivors of pediatric myocarditis. Prolonged follow-up of patients who survive myocarditis is therefore recommended not only to detect possible progression to cardiomyopathy, but also to identify non-cardiac comorbidities.

Keywords: myocarditis, child, celiac disease, cystic fibrosis, Alström syndrome, Kawasaki disease

## Introduction

Although long term outcome studies in large pediatric myocarditis/cardiomyopathy populations have been reported in literature, none of them focused on comorbidities [1-4]. A recent pediatric study showed that children with myocarditis/cardiomyopathy may have celiac disease (prevalence 1.8%) [5]. Another report suggested that celiac disease, which is often clinically unsuspected, accounts for as many as 5-5.7% of adult patients with autoimmune myocarditis [6,7]. Information on possible other comorbidities that may influence recovery is scarce. Prolonged follow-up results presented an opportunity to gather additional information regarding the coexistence of non-cardiac diseases in pediatric myocarditis. The clinical characteristics of patients with pediatric myocarditis treated at the Department of Pediatrics, University of Debrecen were studied to shed new light on the course of this illness and the possible comorbidities.

## Methods

*Patients and data collection*

We retrospectively followed all children and adolescents (age <18 years) with myocarditis treated at the Department of Pediatrics, University of Debrecen, Hungary. Patients suffering from myocarditis during the period 1996–2011 were enrolled. The inclusion criteria were patients with myocarditis who had been followed for the entire period of their cardiac care. Myocarditis was defined as severe cardiac dysfunction or regional wall motion abnormality seen on echocardiography, with the exclusion of other causes such as coronary disease, sepsis, metabolic heart disease, congenital malformation and a history of cardiomyopathy. All the nine study patients had a recent history of viral illness, and the six survivors had complete recovery of their cardiac function. In two of three fatal cases, autopsies were performed, which included histologic evaluation of the heart. Data collection considered all hospital

records, including outpatient notes and hospital progress notes, as well as cardiology and radiology reports.

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## Results

A total of nine children (5 girls and 4 boys) were admitted to the hospital with a diagnosis of myocarditis between January 1996 and December 2011. The median age of the patients was 1.11 years (range 0.03–8.71 years), and the median follow-up time was 11.52 years (range 1.6–16.2 years). The incidence rate of hospital discharges diagnosed with myocarditis at the Department of Pediatrics, University of Debrecen, Hungary was 1/10,000 (1996–2011).

### *Primary clinical symptoms*

The primary symptoms included poor feeding and lethargy in eight patients, tachypnea in six, and chest pain in one 8-year-old child (Table I). This last patient was shown to have peri-myocarditis by non-invasive evaluation. Three of the nine patients were only admitted at their second outpatient visit, because myocarditis was not suspected at their first visit.

### *Cardiology and laboratory findings*

All patients had abnormal electrocardiograms on admission. Each patient had sinus tachycardia and ST-T abnormalities, and four of them showed low voltage. Cardiomegaly was detected in six patients and prominent right atrium in two others by chest x-ray.

Echocardiography detected systolic dysfunction of the left ventricle in eight patients and regional wall motion abnormalities with pericardial effusion in one other. Three patients

with acute fulminant myocarditis had poor ventricular function but no ventricular dilatation. Normal left ventricle size was identified in the patient with recurrent peri-myocarditis. All patients had mitral regurgitation. Cardiac enzymes or troponin were checked in eight patients and were positive in six (Table I).

Myocardial biopsy was not performed in any patients. Among the three fatal cases, histological examinations at autopsy in two showed myocytolysis with acute inflammatory cell (leukocyte common antigen-positive) infiltration in one case, and severe myocytolysis without inflammatory cellular infiltrate in the other. No autopsy was performed in the third case because of the lack of parental informed consent.

Cardiac magnetic resonance imaging (MRI) in one patient with recurrent peri-myocarditis revealed delayed enhancement in the anterior wall of the LV 142 days after the onset of the second episode.

Serology for viruses was performed in each patient. Two patients had acute adenovirus infection and another had influenza A virus infection.

*Acute treatment*

The standard treatment for each patient included furosemide, digoxin and an angiotensin converting enzyme inhibitor. Six of the nine patients received dopamine-dobutamine and one received milrinone infusion. Steroids were administered to two patients during the acute phase because of cardiac shock, and to two other patients during the subacute phase (from days 10–14 of the disease for 60 days). Intravenous immunoglobulin was given to four patients during the acute phase. Mechanical ventilation was administered to three patients. The patient with peri-myocarditis received a non-steroidal antiinflammatory agent (Table II).

*Acute clinical course*

Three patients died of cardiogenic shock during the acute phase of the disease (days 1, 2 and 8 following admission, respectively). The clinical pictures in Patients 5, 8 and 9 fulfilled the diagnosis of acute fulminant myocarditis (Table I-III). One patient subsequently developed a left ventricular thrombus and cerebral embolization, but the intracardiac thrombus resolved after heparin therapy (Patient 2). This patient still had mild residual right-sided hemiparesis 12 years after the stroke. Episodes of atrial tachycardia developed in a newborn and lasted for 5 days. No serious complications occurred during the acute phase of the disease in four cases.

*Left ventricular function*

Recovery from the severe initial left ventricular dysfunction (fractional shortening $\geq$ 30%) in the five survivors took 22–510 days (median 150 days). In the sixth survivor with recurrent peri-myocarditis, regional wall motion abnormalities disappeared on days 11 and 18, respectively. The mitral regurgitation detected on the second occasion had also disappeared by day 18.

None of the survivors developed dilated cardiomyopathy during the follow-up period.

*Long-term follow-up:*

*Patient 1.* A 4-month-old girl (Patient 1) developed heart failure with elevated cardiac enzymes (aspartate aminotransferase and alpha hydroxybutyrate dehydrogenase) and left ventricle dysfunction (Table 3). Her cardiac function improved gradually as a result of anti-congestive treatment including dopamine, and fractional shortening was 30% after 120 days. Her LV size and systolic function remained normal during the next 15 years. However, gradual visual impairment was detected from the age of 2 years, diagnosed as Leber's congenital amaurosis. Hypacusis was detected at age 7 years, which was explained by

respiratory obstruction due to recurrent tonsillitis. She was also evaluated for obesity and dyslipidemia (cholesterol: 8.1 mmol/l, triglycerides 3.7 mmol/l), impaired glucose tolerance (120-min blood sugar 11.1 mmol/l), and latent hypothyreosis (circulating thyroid-stimulating hormone 4.6 mU/l, free thyroxine 11.6 pmol/l). At the age of 11 years, manifest type 2 diabetes mellitus was diagnosed (fasting blood sugar 17.5 mmol/l) and diet therapy and metformin were initiated. Based on a review of her symptoms, Alström syndrome was verified.

*Patient 2.* This patient developed a left ventricular thrombus and cerebral embolization during the acute phase of the disease. The intracardiac thrombus resolved with heparin therapy, but the patient still had mild residual right-sided hemiparesis 12 years after the stroke.

*Patient 3.* This 11-month-old boy, whose left ventricle function recovered within 150 days, was examined 8 years later because of abdominal pain and iron-deficiency anemia. Anti-endomysium antibody (EMA) positivity indicated duodenal biopsy, which revealed gluten-sensitive enteropathy with subtotal atrophy (Stadium Mars IIIb). Left ventricle size and fractional shortening were normal when the diagnosis of celiac disease was established. A gluten-free diet resulted in resolution of the iron-deficiency anemia and accelerated growth. At the onset of myocarditis, the child was already exposed to a gluten-containing diet.

*Patient 4.* This 8-year-old boy with peri-myocarditis characterized by chest pain and a high troponin I level (115.9 μg/l) recovered within 2 weeks. Myocardial perfusion scintigraphy was performed with negative results. A complete blood count was within the normal range though mean corpuscular volume was 75 femtoliters (fL). Seven years later, the symptoms of peri-myocarditis recurred with high troponin T (4892 ng/l) and elevated pro-brain natriuretic peptide levels (245 pmol/l). Coronary computed tomography ruled out ischemic heart disease. The patient's symptoms disappeared after 3 weeks, but endomysial antibody and tissue transglutaminase antibody tests performed because of anemia (hemoglobin: 117 g/l,

hematocrit: 0.37, mean corpuscular volume: 63.0 fL) revealed positive results. Duodenal biopsy confirmed the diagnosis of celiac disease.

*Patient 7.* Normalization of left ventricle function took 510 days in this 1-year-old infant. A persistent cough, despite an improving trend in cardiac function, prompted us to investigate other etiologies. Forty days after the diagnosis of myocarditis, a sweat test proved positive and genetic evaluation revealed two heterozygous mutations of the cystic fibrosis transmembrane conductance regulator gene (2184insA in 13a exon and deltaF508) (compound heterozygosity), indicating cystic fibrosis.

*Patient 9.* This 8-day-old neonate (body weight 3 kg) was admitted because of fever, poor appetite and extreme drowsiness. ST elevation was seen in most leads on electrocardiogram. Echocardiography revealed pulmonary hypertension, and mild tricuspid and mitral regurgitation. Systolic function of the left ventricle was normal. Decreased left ventricle function (fractional shortening: 23%) and a dilated left main (3.3 mm) coronary artery were detected on day 3 of his admission. Abdominal ultrasound revealed gallbladder hydrops. On the same day, high cardiac troponin T was detected (10,761 ng/ml), and C-reactive protein was 3.09 mg/l. The thrombocyte count was $159 \times 10^9$/l, which had risen to $446 \times 10^9$/l 10 days later. A stool adenovirus antigen test was positive. Because incomplete Kawasaki disease could not be ruled, out intravenous immunoglobulin was administered (2 g/kg). Atrial ectopic tachycardia (180–220/min) developed on day 4, resulting in heart failure. Amiodarone and milrinone were introduced. Episodes of atrial tachycardia lasted for 5 days. Left ventricle function recovered by day 25 after admission, and by the age of 1 year, no coronary dilatation or structural heart disease were detectable.

## Discussion

This study demonstrated a cross-section of clinical scenarios characterized by severe heart failure, with acute myocarditis as the most likely diagnosis. It was notable that, in four of six

long-term survivors, myocarditis preceded the manifestations of other non-cardiac, genetically-determined chronic pediatric diseases. Although simple coincidence cannot be ruled out, the patients' altered genetic characters raise the possibility of an association between these conditions.

Recurrent pericarditis in celiac disease has already been reported in a previous study [8]. In one patient in the current study, high troponin levels and cardiac MRI verified recurrent peri-myocarditis with residual fibrosis. Curione et al. showed an increased prevalence of celiac disease in patients with dilated cardiomyopathy [7], while another report suggested that celiac disease, which is often clinically unsuspected, accounts for as many as 5% of patients with autoimmune myocarditis [6]. Regarding the relationship between celiac and cardiac diseases, Elfström et al. found no significant correlation with previous myocarditis [9]. It is notable that the median age at the diagnosis of celiac disease was 2 years, suggesting that a timely diagnosis may have prevented the development of cardiac disease. A recent pediatric study showed that children with myocarditis/cardiomyopathy may have celiac disease (prevalence 1.8%) [5].

The association between prior myocarditis in patient 3 (an 11-month-old boy) and a manifestation of celiac disease 8 years later is questionable. The child was already exposed to a gluten-containing diet at the onset of myocarditis. However, because the duration of the mechanism leading up to alterations in the myocardium in celiac disease is unknown, a relationship between these two conditions cannot be ruled out.

Patient 1 in the present study fulfilled the diagnostic criteria for Alström syndrome [10], which is a rare autosomal recessive genetic disorder encompassing cone-rod dystrophy in infancy, hearing loss, childhood truncal obesity, hyperinsulinemia and type 2 diabetes mellitus, hypertriglyceridemia, short stature in adulthood, dilated cardiomyopathy, and progressive pulmonary, hepatic, and renal dysfunctions, with development of multiple-organ fibrosis [11]. Cardiomyopathy occurs in two-thirds of these patients. Heart failure has two

forms: infantile and adult-type onset cardiomyopathies [11]. Many of these infants can have apparent recovery of cardiac function for decades [12]. Michaud et al. performed myocardial biopsies in two cases and failed to detect inflammatory infiltrates [12], and although endomyocardial biopsy is the gold standard for the diagnosis of myocarditis, its sensitivity is controversial [13, 14]. However, acute heart failure in infancy that subsequently recovers suggests the possibility of myocarditis. Acute heart failure in our patient with Alström syndrome was preceded by fever and upper respiratory symptoms. Poor ventricular function on echocardiography was associated with elevated levels of cardiac enzymes. However, their cardiac function recovered completely and remained normal for 15 years. Although endomyocardial biopsy was not performed, this case was highly suggestive of myocarditis.

Alström syndrome is a ciliopathy. Primary cilia transport signaling molecules and receptors up and down their lengths via intraflagellar transport [15]. The Coxsackie virus adenovirus receptor plays an important role in pediatric myocarditis [16], and altered cilial function may result in changes in Coxsackie virus adenovirus receptor function.

In the present study, the diagnosis of acute myocarditis was based largely on clinical features and echocardiographic changes, while electrocardiogram and biological markers served as additional non-invasive diagnostic modalities. Complete recovery on long-term follow-up also confirmed the diagnosis of myocarditis.

Compromised natural protective factors are likely to play a pathogenetic role in cystic fibrosis, while autoimmune mechanisms may be involved in cases with celiac disease. Myocarditis or peri-myocarditis may precede the clinical manifestation of celiac disease. The onset of severe cardiac dysfunction in infancy, which subsequently resolves, raises the possibility of myocarditis as the initial manifestation of Alström syndrome. No association between myocarditis and cystic fibrosis has been described previously. Genetic abnormalities, including those involving the HLA-DQ locus, may create susceptibility to myocarditis via

direct or indirect mechanisms. The markedly long time to left ventricle recovery (120–510 days) might have been associated with the presence of comorbidities in three patients.

## Limitations

This study had some limitations. Firstly, it was based on a small sample size and was a purely descriptive study. The inclusion criteria were based mainly on clinical features. Endomyocardial biopsy and thorough virus analysis including polymerase chain reaction analysis would have made the evaluation more comprehensive. However, the prolonged follow-up period ruled out most alternative diagnoses (e.g., metabolic cardiomyopathies). Nonetheless, even if the diagnosis of myocarditis is questionable, the observation that severe heart failure and systolic dysfunction (or regional wall motion abnormality) preceded the manifestation of non-cardiac pediatric diseases is noteworthy.

## Conclusions

In conclusion, to the best of our knowledge, this represents the first pediatric study with a prolonged follow-up period focusing on the comorbidities associated with myocarditis. The results suggest that myocarditis may precede the manifestations of other chronic pediatric diseases, though the pathophysiologies are likely to be heterogeneous. Prolonged follow-up of patients who survive myocarditis is therefore recommended not only to detect possible progression to cardiomyopathy, but also to identify non-cardiac comorbidities.

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Table I Characteristics of patients on admission

| Patient | Age on admission (year) | Gender | Symptoms (onset prior admission) | Initial FS % | Initial LVEDD mm (Ref. value) | Initial MI | Low voltage on ECG | CK/Tn rise | Viral agent |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 0.58 | female | fever, tachypnea (3 days) | 7 | 32 (18-26) | yes | yes | yes | |
| 2 | 1.21 | male | rhinorrhea, cough, lack of appetite (60 days) | 10 | 47 (22–32) | yes | no | no | |
| 3 | 0.89 | male | rhinorrhea cough, lack of appetite (60 days) | 10 | 51 (21–31) | yes | no | no | |
| 4 | 8.71 | male | chest pain (1 day) | 31 | 39 (31–43) | no | no | yes | influenza A |
| | 15.69 (at recurrence) | | chest pain (1 day) | | 49 (37–49) | yes | yes | yes | |
| 5 | 1.5 | female | diarrhea, fatigue (3 days) | 19 | 29 (22–32) | yes | no | yes | adeno |
| 6 | 1.45 | female | diarrhea, lack of appetite, fatigue (4 days) | 8 | 42 (21–31) | yes | yes | not checked | |
| 7 | 1.11 | female | rhinorrhea, cough, lack of appetite, fatigue (14 days) | 6 | 40 (21–31) | yes | yes | yes | |
| 8 | 0.25 | female | tachypnea, fatigue (6 h) | 13 | 25 (17–25) | yes | yes | yes | |
| 9 | 0.03 | male | fever, drowsiness, hypotonia (12 h) | 23 | 20 (15–21) | yes | no | yes | adeno (stool) |

*Abbreviations:* FS = fractional shortening, LVEDD = left ventricular end diastolic dimension (M-mode), MI = mitral insufficiency, ECG = electrocardiography, CK/Tn = creatine kinase/troponin I or T, adeno = adenovirus

**Table II** Treatment and hospital course

| Patient | Intravenous inotropic support | Use of IVIG | Mechanical ventilation | Circulatory arrest | Other major event | Death | ICU LOS (days) | Hosp LOS (days) |
|---|---|---|---|---|---|---|---|---|
| **1** | yes | no | no | no | | no | 7 | 20 |
| **2** | yes | no | no | no | LV thrombus | no | 20 | 56 |
| **3** | no | no | no | no | | no | 6 | 18 |
| **4** | no | no | no | no | | no | 4 | 7 |
| | no | yes | no | no | | no | 6 | 10 |
| **5** | yes | no | yes | yes | | yes | 2 | 2 |
| **6** | yes | no | yes | yes | | yes | 2 | 3 |
| **7** | yes | yes | no | no | | no | 16 | 41 |
| **8** | yes | yes | yes | yes | | yes | 1 | 1 |
| **9** | yes | yes | no | no | AET | no | 20 | 30 |

*Abbreviations:* IVIG = Intravenous immunoglobulin, ICU LOS = intensive care unit length of stay, Hosp LOS = hospital length of stay, LV = left ventricle, AET = atrial ectopic tachycardia

Table III Long-term follow-up

| Patient | Age at disease onset (years) | Complications during acute course | Time to recovery of LV function* (days) | Follow-up duration (years) | Late outcome | Associated non-cardiac disease revealed during follow-up |
|---|---|---|---|---|---|---|
| **1** | 0.58 | - | 120 | 16.2 | complete cardiac remission | Alström syndrome 8 years later |
| **2** | 1.21 | LV thrombus, cerebral embolization | 300 | 13.78 | complete cardiac remission mild hemiparesis | |
| **3** | 0.89 | - | 150 | 13.71 | complete cardiac remission | celiac disease 9 years later |
| **4** | 8.71<br>15.69 | peri-myocarditis | 11<br>18 | 9.32 | 7 years later recurrent peri-myocarditis | celiac disease 7 years later |
| **5** | 1.5 | death 2 days | | | | |
| **6** | 1.45 | death 3 days | | | | |
| **7** | 1.11 | | 510 | 4.57 | complete cardiac remission | cystic fibrosis 1 month later |
| **8** | 0.25 | death 10 h | | | | |
| **9** | 0.03 | atrial ectopic tachycardia | 22 | 1.6 | complete cardiac remission | |

*Abbreviations:* LV = Left ventricle, *fractional shortening ≥30% and normalization of LV size or cessation of wall motion abnormality