Exercise-triggered chest pain as an isolated symptom of myocarditis in children

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Abstract

In childhood, chest pain occurring at exercise is a common complaint. A cardiac etiology for it is exceptionally found, explaining that most children do not undergo systematic cardiological investigation. However, chest pain at exercise may manifest as the unique symptom of a viral myocarditis. Recognizing this form of myocardial injury, however, might help to avoid clinical deterioration by providing adequate care. In this paper, we report on two children presenting with the unique clinical symptom of chest pain related to physical activity and in whom laboratory and cardiac investigations suggested transient myocardial damage related to myocarditis.

Introduction

Chest pain is a common complaint in children and is most frequently benign. In about 2% of the cases however, it has a cardiac origin such as a valvular- or a coronary anomaly, a pericarditis or a myocarditis.[1]

Myocarditis is an inflammatory disease of the myocardium mostly due to viral infection. Clinical manifestations of viral myocarditis in children vary from isolated chest pain to severe cardiac failure due to dilated cardiomyopathy, a severe condition that might require invasive cardio-pulmonary support including extracorporeal assistance and cardiac transplantation or sudden death.[2,3]

We report on 2 otherwise healthy children who consulted at an interval of 2 weeks in our department because of acute chest pain occurring at exercise and in whom transient myocardial cell damage was assessed. The diagnosis of pauci-symptomatic viral myocarditis was suggested.

Case Reports

Case #1

A 10-year old boy without any relevant familial or personal medical history was admitted in the emergency department in early spring because of a first episode of retrosternal chest pain irradiating in the left shoulder during a football match. Chest pain ceased after he had interrupted exercise. There was no recent history of infection.

Clinical examination was normal. Blood pressure was 105/53 mmHg and heart rate 70/minute.

Electrocardiogram (ECG) at admission revealed repolarization abnormalities with ST-segment elevation in V3.

Laboratory examinations showed ultrasensitive troponin T serum concentration of 282 ng/L (normal: <14 ng/L). Leukocyte count (8170/ mm^3) and concentration of C-reactive protein (<0.1 mL/L) were in normal range.

Four hours later, ECG showed ST-segment elevation in V2 and V3 (Figure 1). Troponin T concentration increased up to 660 ng/L.

Echocardiography was normal, in particular, the origin and course of the coronary arteries. There was no pericardial effusion.

During his hospital stay, the patient was stable at rest. There were no cardiac dysrhythmias at continuous cardiac monitoring at any time. ECG (Figure 1) and troponin T levels normalized in the next 48 h.

Cardiac resonance magnetic imaging (CMR) performed at day 3 confirmed the absence of cardiac anomaly but demonstrated a small pericardial effusion anterior to the right ventricle (Figure 2). There were no signs of myocardial inflammation or ischemia.

Coronarography was performed at day 4 that permitted to definitively exclude coronary anomaly and coronary compression by myocardial bridge.

Serum titer of antibodies against coxsackie and echovirus rose from 32 at the time of admission to 128 at control examination 4 weeks later, revealing recent viral infection. Serum titers of antibodies against adenovirus, influenza A and B, parainfluenza 1, 2, 3, parvovirus B19, Epstein Barr virus and cytomegalovirus were negative.

The patient was discharged without any treatment but the recommendation to avoid physical activity for 4 weeks until the control examination. At that time, he was free from any complaint. Clinical examination, echocardiography as well as ECG at rest and at exercise, and troponin T levels after exercise were normal.

The patient was allowed to go back to his normal activity including football training. At 1-year follow-up, ECG at rest and at exercise and echocardiography were normal.

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Case #2

A 7-year old boy was examined in the outpatient clinic in early spring for transient retrosternal chest pain that occurred a couple of days before during sport and recurred the day of examination while the patient was at rest.

His personal history was uneventful. There was no recent history of infection.

Clinical examination was normal. Blood pressure and heart rate were 102/58 mmHg and 75/min, respectively.

ECG showed first-degree atrio-ventricular block and ST-segment elevation in DII, DIII and aVF (Figure 3A).

Echocardiography including the verification of the origin and course of the coronary arteries was normal. There was no pericardial effusion.

Laboratory examinations showed elevated ultrasensitive troponin T concentrations: 147 ng/L (normal: <0.14 ng/L). Leukocytes count (11,600/mm^3) and C-reactive protein (<0.2 mg/L) were in normal range.

At CMR performed at day 3, structural or functional myocardial- and coronary artery anomalies were excluded. For that reason, coronarography was not performed. Serum titers of antibodies against adenovirus, coxsackies and echovirus, parvovirus B19, Epstein Barr virus, Influenza A and B virus, parainfluenza 1, 2 and 3 virus, acquired immunodeficiency syndrome virus, chlamydia and

mycoplasma were all negative.

The patient was observed for 48 h until repolarization anomalies disappeared at ECG (Figure 3B) and troponin-T values returned to normal. He was discharged with the recommendation to avoid physical activity for 4 weeks until control examination. ECG at rest and at exercise, and troponin T values after exercise on that occasion were normal. Thus, the boy returned to his normal activity. At 1-year follow-up, ECG at rest and at exercise and echocardiography were normal.

Discussion

We report the case of 2 children who consulted for retrosternal chest pain occurring at physical exercise. They were previously in good general condition allowing them to participate to regular intensive sport training. Both had repolarization anomalies at rest ECG and significantly elevated troponin T concentrations without any biological sign of inflammation. ECG anomalies and troponin T levels normalized in the first 2 days after admission.

Repolarization anomalies at ECG and troponin T elevation are the hallmark for myocardial cell damage whatever the cause is.[4] Acute myocardial cell damage in children with so far uneventful medical history is exceptional.[5] It might be due to congenital or acquired coronary anomalies, *i.e.*, an anomalous origin of a coronary artery such as the anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA),[6] sequels of a Kawasaki disease,[7] or inflammatory lesions to the myocardium.[3] These conditions might all be revealed by chest pain at exercise.

An anomalous origin of a coronary artery such as ALCAPA manifests more frequently in infants by signs of congestive heart failure and/or myocardial infarction.[6] Vascular, in particular coronary sequels of Kawasaki disease might remain unrecognized in young children. Indeed, Kawasaki disease is a challenging diagnosis and not all patients affected by the disease undergo echocardiography. Furthermore, late coronary sequels may occur.[7] Functional coronary stenosis secondary to muscular bridges in patients with myocardial hypertrophy or to a compression of a coronary artery between aorta and pulmonary arterial trunk may manifest by inaugural myocardial ischemia.[8] Selective coronarography was performed in the first patient to exclude with the last certitude such a coronary anomaly.

Troponin T is the subunit of the troponin complex that shows the highest sensibility and specificity with regard to myocardial cell damage.[5,9] Its serum levels rise in the first 4 days after injury and stay elevated for 6-14 days,[9] correlating with the extend of injury.[4]

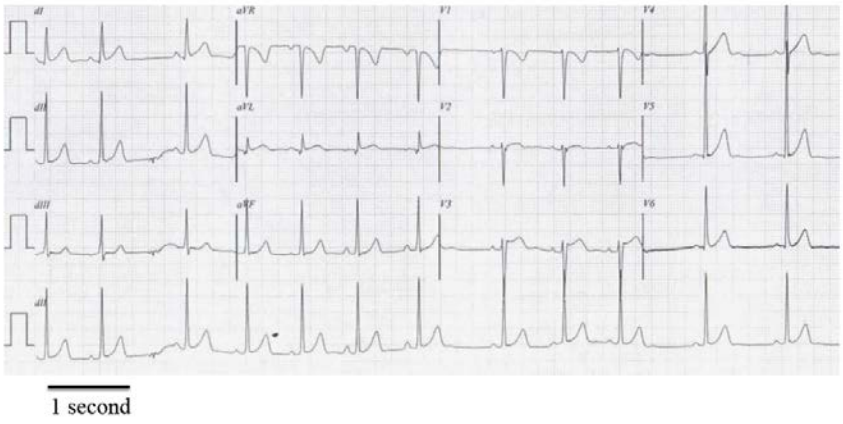

Figure 1. Electrocardiogram of patient 1 registered at admission. ST segment is elevated in lead V3. 25 mm/s; 10 mm/mV.

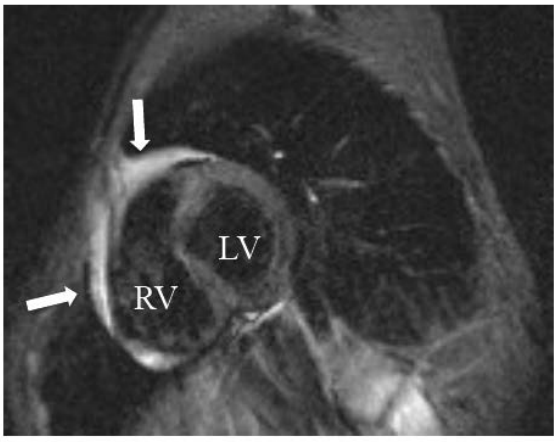

Figure 2. Cardiac magnetic resonance imaging performed in patient 1 showing normal finding but a small pericardial effusion in front of the right ventricle (arrows).

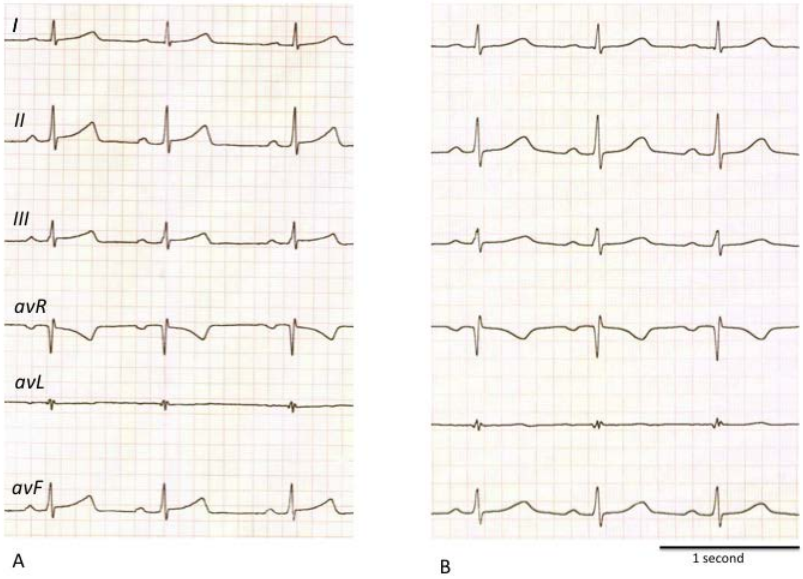

Figure 3. Electrocardiogram registered at admission in patient 2, showing ST-elevation in leads II, III and avF (A) and 48 h later (B) showing normal findings. First-degree auriculo-ventricular block is physiologic. 50 mm/s; 10 mm/mV.

In the case of a viral myocarditis, troponin T is early released into the blood circulation, before biological signs of inflammation, if any, appear.[5] This makes troponin T determination an essential diagnostic tool in all cases of suspected myocardial injury although elevated levels are not specific of the cause of myocardial cell damage.[10]

In both patients reported here, echocardiography showed normal parameters of systolic function and was therefore not contributive for the diagnosis of myocarditis. Echocardiography remains, however, central for the diagnosis of all conditions where myocardial injury is suspected, allowing the exclusion of most of its causes.[11] Nevertheless, if present, abnormal contractility patterns are non-specific for the cause of myocardial injury and require to be investigated by other means.

In this respect, CMR is superior to echocardiography for the diagnosis of myocarditis.[2,11,12] It allows evaluating different markers of tissue injury: edema, hyperemia, necrosis and fibrosis.[13,14] Myocardial edema is visualized in T2-weighted sequence. Hyper-perfusion and capillary leakage are shown in T1-weighted sequence and by early gadolinium enhancement while necrosis and fibrosis are shown as late enhancement due to the penetration of gadolinium into the intracellular space of damaged cardiomyocytes. Furthermore, sub-epicardial- and intra-myocardial late enhancement suggests myocardial fibrosis related to myocarditis while sub-endocardial late enhancement suggests ischemic injury.[12] CMR is therefore a useful tool in discriminating 2 different causes of myocardial damage with similar clinical manifestations. In our patients, CMR was normal except for a small pericardial effusion in the first one, suggesting that in both cases the degree of myocardial injury was not sufficient to allow its detection by CMR.[2]

While myocardial biopsy remains the gold standard for the definitive diagnosis of myocarditis, its routine use in children is limited by its invasiveness and its related complications such as myocardial perforation, pericardial tamponade, dysrhythmias and death.[14] Furthermore, the histological interpretation is conditioned by the biopsy size and the patchy characteristics of myocardial lesions. In fact, the indication of myocardial biopsy is limited to fulminant cases or those with severe arrhythmias.[15]

For these reasons, the presence in the serum of specific antibodies directed against the virus involved in the pathophysiology of myocarditis is commonly investigated in children. It must however be pointed out that in the majority of cases, the pathogen responsible for proven myocarditis cannot be identified by serum titers. Indeed, in a recent study, the virus identified by the presence of its genome in myocardial biopsies could not be identified by serological titers except in 4% of the patients.[16] In accordance to that, viral serum titers were negative in our second patient. The combination of transient ECG anomalies and troponin T elevation as a marker for myocardial cell injury in both patients, and coxsackie and echovirus serum titer increase in the 1st one, let us conclude to a pauci-symptomatic viral myocarditis in both cases. This form of viral myocarditis is challenging to diagnose but important due to the fact its long-term outcome is not known.[17]

The degree of severity of clinical manifestations of viral myocarditis depends on the pathophysiological mechanisms and the virus involved. Coxsackie B, echovirus, adenovirus, parvovirus B19 and human herpes virus 6 are the most commonly identified virus with a tendency of increasing incidence of non enteroviruses and decreasing incidence of enteroviruses in the last 2 decades.[2,11,17] Upon myocardial infection, the disease evolves classically in 3 phases with some variability explaining the large spectrum of clinical manifestations.

In the acute viral phase, virus injures myocardial cells leading to cell lysis and activation of the innate immunity. In most patients, viruses will be eliminated at that stage and the inflammatory response will be regulated and shortly terminated without any sequel of cardiomyocyte injury. This phase is often asymptomatic. The subacute phase results from the inefficacity to eradicate the virus. It is associated with the activation of the acquired immunity. In most cases, the inflammatory reaction diminishes while viruses are eliminated and myocardial function recovers with myocardial tissue repair. However, experimental murine models showed that despite the absence of viral genome, autoimmune processes take place that are characterized by molecular mimicry allowing antibodies to be directed against myosine or β-adrenergic receptors.

Finally, the myopathy phase is characterized by myocardial remodeling as a result of inflammation, cell death and fibrosis that leads to dilated cardiomyopathy.[17]

Viruses such as parvovirus B19 and cytomegalovirus have the potential to injure not only cardiac myocytes but also endothelial cells of the coronary microcirculation,[18] leading to endothelial dysfunction and coronary vasoconstriction. This explains chest pain patients with viral myocarditis may complain about and the anomalies observed at ECG that might be interpreted as signs of myocardial infarction.[17] Our patients had as unique symptom chest pain that was elicited by physical activity, indicating inadequate coronary blood supply. Besides increased coronary demand, physical activity in patients with viral myocarditis could also contribute to higher mortality by modifying the balance between type-1 and type-2 T lymphocytes. Indeed, severe exercise has been related to decreased type 1 T-cell cytokine production, thus impairing protection against viral infections.[19] This could be the explanation for the increased viral replication and mortality related to severe exercise observed four decades ago in mice with coxsackie myocarditis.[20] For these reasons, physical activity must be avoided in acute myocarditis.[2] Up to now, there are no recommendations available for the follow-up and the duration of sport abstinence in children with pauci-symptomatic viral myocarditis. In the cases reported here, we arbitrarily recommended a period of sport abstinence of 4 weeks until control examination was performed that confirmed fully normalization of rest- and stress-ECG.

Conclusions

Clinical presentation of viral myocarditis in children varies depending on the degree of myocardial and endothelial injury. Chest pain at physical exercise can be the unique manifestation of this potentially severe myocardial disease. In order not to miss pauci-symptomatic forms that require adequate advice and follow-up control, cardiac exploration with at least ECG should be performed in all cases of chest pain occurring at physical exercise in children.

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