Human enteroviruses and parechoviruses: disease spectrum and need for treatment in young children
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Chapter 9

Successful IVIG treatment of human parechovirus-associated dilated cardiomyopathy in an infant

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Abstract

Human parechoviruses (HPeVs) are closely related to human enteroviruses and exhibit many similarities in disease spectrum and symptoms. HPeV1 is most commonly associated with mild disease, but rare associations with severe disease such as myocarditis have been reported. Currently, no treatment is available for severe HPeV infections.

In this case report we describe an infant with a severe dilated cardiomyopathy in whom HPeV1 was revealed to be the only identifiable cause. The infant was treated with intravenous immunoglobulins (IVIGs) and recovered completely. *In vivo* blood samples revealed a high HPeV1 antibody titer after treatment with IVIGs. *In vitro* IVIGs contained high titers of neutralizing antibodies against HPeV1.

Our hypothesis is that patients with myocarditis caused by viruses with a high prevalence in the population and hence high antibody titers in IVIGs are likely to benefit from treatment with IVIGs. More research, combining virological and clinical data, is needed to see whether this hypothesis is true.
Introduction

Human parechoviruses (HPeVs) are closely related to human enteroviruses (HEVs) and both belong to the *Picornaviridae* family. HPeVs exhibit many similarities to HEVs in symptoms and spectrum of disease.\(^1\,^2\) HPeV1 and HPeV3 are the most common types of the currently known 16 subtypes, mainly infecting young children under the age of 2 years.\(^1\,^3\,^4\) HPeV3 is associated with meningitis and sepsis-like illness especially in neonates and children aged <6 months,\(^5\,^6\,^7\) whereas HPeV1 usually causes mild gastrointestinal and respiratory disease, although meningitis and sepsis-like illness may occur.\(^5\) As incidentally reported in case reports and small studies, HPeV1 has been associated with myocarditis,\(^9\,^10\) encephalitis,\(^11\) encephalomyelitis,\(^12\) acute flaccid paralysis,\(^13\) sudden infant death,\(^14\) and necrotising enterocolitis.\(^15\) The prevalence of HPeV1 is high in young children.\(^3\,^4\,^16\) As was revealed in a longitudinal study, most children become seropositive before the age of 2 years.\(^17\) In adults, 95 to 99% have antibodies against HPeV1.\(^17\) Symptomatic HPeV infection in adults is rarely reported. Currently there is no treatment available for severe infections with HPeV (reviewed in Tauriainen \textit{et al.}\(^18\)). In neonates with severe HEV infections intravenous immunoglobulins (IVIGs) is randomly provides, with various outcomes. Given the similarity between HPeVs and HEVs it seems rational to provide IVIGs to neonates/infants with severe HPeV infection as well.\(^18\)

In this case report we describe for the first time an infant with myocarditis and dilated cardiomyopathy due to an HPeV1 infection who was successfully treated with IVIGs.

Patient presentation

A 5-month-old boy was admitted to the PICU with circulatory insufficiency due to suspected myocarditis.

The medical history of the boy was unremarkable until the age of 3 months. He was born at term after an uncomplicated pregnancy. He was growing adequately, but excessive perspiration was visible during feedings. On admission, the patient was pale, markedly dyspneic, and irritable, with a heart rate of 180 beats per minute and a respiratory rate of 40 breaths per minute. His temperature was normal. The patient’s oxygen saturation was 94% and blood pressure was 88/58 mm Hg. Examination of the heart revealed soft heart sounds without audible extra heart sounds, no mitral regurgitation murmur and an enlarged heart with percussion. The lungs and abdomen revealed no abnormalities. The chest radiograph revealed an enlarged heart. The electrocardiogram showed sinus tachycardia, normal axis, and abnormal repolarisation with no signs of ischemia.

The first laboratory evaluation revealed elevated cardiac enzymes without other deviations or signs of infection (Table 1).
An echocardiogram was performed and showed a severely dilated left ventricle with a shortening fraction of 3% and a left ventricle end-diastolic diameter (LVED) of 202% (Fig. 1). No structural abnormalities possibly leading to left ventricular failure were detected, suggesting a viral cause of the dilated cardiomyopathy.

Supportive treatment with milrinone, dobutamine and diuretics was started. A 3-day course of 2 g/kg IVIGs was started because a viral cause of myocardiopathy was suspected and no other treatment options were available. HPeV was detected in blood and feces by 5' untranslated region (UTR) polymerase chain reaction (PCR),\(^1\) which was revealed to be an HPeV1 by molecular typing.\(^2\) No other viruses were detected at the time of diagnosis except for a very low cytomegalovirus (CMV) viral load in blood (<1000 copies/mL), which was considered clinically irrelevant. Positive Epstein-Barr virus and CMV IgG antibodies were interpreted as the result of transmission of maternal IgG antibodies. Serological tests for Coxsackievirus B, herpes zoster virus, herpes simplex virus, mycoplasma and mumps were negative. A cardiac biopsy was not performed.

Metabolic diseases were evaluated and excluded; genetic diseases causing cardiac disease were considered not likely by a specialist in genetic diseases.

In the following days digoxine and an angiotensine-converting enzyme inhibitor were added to support cardiac functions. One week after the start of IVIG treatment, the patient’s clinical condition improved.

Cardiac functions improved with a shortening fraction of 10.5%. Although LVED remained unchanged, a significant decrease in N-terminal pro b-type natriuretic peptide (NT-pro-BNP) from 67 000 to 5000 ng/L implied reduced left ventricular filling pressures. In the following weeks the boy continued to recover and cardiac function improved steadily. After 1 month HPeV could not be detected by PCR in the blood, whereas HPeV shedding in faeces occurred until 2 months after admission.

### Table 1. Patient’s laboratory results on admittance.

<table>
<thead>
<tr>
<th>Marker</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin, mmol/L</td>
<td>6.3</td>
</tr>
<tr>
<td>Leukocytes, 10^9/L</td>
<td>11.3</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>7.72</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>3.31</td>
</tr>
<tr>
<td>Thrombocytes, 10^9/L</td>
<td>415</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>1</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>143</td>
</tr>
<tr>
<td>Potassium, mmol/L</td>
<td>5.1</td>
</tr>
<tr>
<td>Calcium, mmol/L</td>
<td>2.31</td>
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<tr>
<td>Magnesium, mmol/L</td>
<td>0.98</td>
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<tr>
<td>Serum urea nitrogen, mmol/L</td>
<td>4.6</td>
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<tr>
<td>Creatinine, µmol/L</td>
<td>23</td>
</tr>
<tr>
<td>ALAT, U/L</td>
<td>16</td>
</tr>
<tr>
<td>ASAT, U/L</td>
<td>40</td>
</tr>
<tr>
<td>CPK, U/L</td>
<td>64</td>
</tr>
<tr>
<td>CKMB, µg/L</td>
<td>6.7</td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
<td>3.2</td>
</tr>
<tr>
<td>Troponine T, µg/L</td>
<td>0.178</td>
</tr>
<tr>
<td>NT-Pro-BNP, ng/L</td>
<td>67106</td>
</tr>
</tbody>
</table>

ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase. CPK, creatine phosphokinase; CKMB, Creatine kinase MB isoenzyme; NT-pro-BNP, N-terminal pro b-type natriuretic peptide.
In addition, HPeV1-specific antibody titers were determined in blood, showing a negative titer (<8) on admittance, an increase in antibody titer to 512 directly after treatment with IVIGs and a residual antibody titer of 32 after 1 month. Earlier results from our laboratory revealed a high titer of HPeV1-specific antibody titers in IVIGs.\textsuperscript{22}

Cardiac medication was gradually reduced, and after 6 weeks the boy was discharged. Cardiac function was normalized with a shortening fraction of 32\% and an LVED of 115\% on echocardiographic follow-up 6 months later.

\begin{figure}
\centering
\includegraphics[width=0.45\textwidth]{figure1a.png}
\caption{Figure 1. Echocardiography showing a profound dilatation of the left ventricle (A, B) and mitral regurgitation (B).}
\end{figure}
Discussion

In this case report we describe for the first time an infant diagnosed with severe myocarditis and dilated cardiomyopathy associated with HPeV1 who was treated successfully with IVIGs. To our knowledge, myocarditis due to HPeV1 has been described only twice. Maller et al. described a child aged 14 months old who died of myocarditis. Echovirus 22 (later reclassified as HPeV1) was cultured from the myocardium and pericardial fluid. The child was thought to have an immunological deficiency because of recurrent infections in the past and the unusual course of this echovirus 22 infection. Antibody production against echovirus 22 was not measured in this patient. Russell and Bell described a 6-week-old boy with a myocarditis (diagnosis based on clinical examination and electrocardiogram) treated with digoxin, steroids and antibiotics. The boy fully recovered within 2 weeks. Blood cultures remained negative. A faeces sample taken 13 days after onset of illness showed echovirus 22 (HPeV1). Low titers of antibodies against Coxsackievirus group B (1-6) as well as echovirus 22 were detected on day 11. A subsequent increase in antibody titers against echovirus 22 to >512 suggested recent infection with this particular virus.

There are no uniform diagnostic criteria for myocarditis in the absence of an endomyocardial biopsy. In a recent seminar (described by Sagar et al.) a 3-tiered classification is proposed. In the absence of another cause, an otherwise unexplained increase in troponin concentrations, electrocardiographic changes suggestive of acute myocardial injury, or abnormal function on echocardiogram or cardiac MRI in combination with a recent trigger for myocarditis (eg, recent viral illness), the possible diagnosis of subclinical myocarditis can be made. Our patient had a (viral) respiratory infection a week earlier. If a patient meets the above mentioned criteria and in addition has acute heart failure or chest pain or (pre) syncope or myopericarditis, the diagnosis is probable acute myocarditis. If myocarditis is confirmed by histological studies, the diagnosis is definite myocarditis. Our patient fulfills the criteria for probable myocarditis (the highest diagnostic category without cardiac biopsy). In addition, parechovirus was isolated from the blood and feces, suggesting disseminated viral disease.

HEVs and more specific Coxsackieviruses are well known to cause myocarditis and/or cardiomyopathy in children. However, in a considerable number of patients no direct cause is found. A retrospective study by Arola et al. in 33 children and adolescents with end-stage dilated cardiomyopathy revealed a positive PCR for HEV in myocardial material in only 1 patient, although the authors were able to detect cellular mRNA in the samples for 32 patients. In another retrospective study by Martin et al., a viral cause could be detected in 26 out of 38 myocardial tissue samples of 34 children with acute cardiomyopathy. Adenovirus was most frequently detected in 15 samples followed by HEV in 8 samples.
Only HEVs, adenoviruses, herpes simplex virus types 1 and 2, and CMV were tested in this retrospective study. In addition, in adults with myocarditis and/or dilated cardiomyopathy, parvovirus B19 has been found in a number of patients (reviewed in Dennert et al.\textsuperscript{26}). The role of different viruses in the pathogenesis of myocarditis in children remains unclear.

Treatment options for acute viral myocarditis/cardiomyopathy are limited. Especially in children, administration of IVIGs is a commonly used treatment option.\textsuperscript{27} A systematic review of the use of IVIGs in viral myocarditis reported only 1 randomized controlled trial in adults and some additional studies of various designs. In many cases, a viral cause of myocarditis could not be directly demonstrated and routine usage of IVIGs for acute myocarditis was therefore not recommended.\textsuperscript{28}

Freund et al.\textsuperscript{29} reported on 7 neonates with HEV myocarditis and reviewed the literature. Only 4 of 35 neonates with HEV myocarditis received IVIGs (3 of them were also treated with pleconaril). Two patients died and only 1 patient recovered completely. The mortality rate was 32% and 58% of the survivors developed severe cardiac sequelae.

In a study by Dennert et al.\textsuperscript{30} in adults with idiopathic cardiomyopathy for at least 1 year, 2 g/kg IVIGs were given to 15 patients with an endomyocardial, biopsy-proven, high parvovirus B19 load. Parvovirus B19 is highly prevalent in the general population and hence a high antibody titer against Parvovirus B19 in IVIGs was expected. A significant decrease in parvovirus B19 load and improvement in cardiac function was seen 6 months after treatment.

We showed \textit{in vitro} that IVIGs contain high titers of neutralizing antibodies against HPeV1.\textsuperscript{22} \textit{In vivo}, our patient’s blood samples revealed an important increase in HPeV1 antibody titers after treatment with IVIGs. These results are in accordance with the marked clinical improvement of our patient after treatment with IVIGs.

Our hypothesis is that patients with myocarditis caused by viruses with a high prevalence in the population and hence high antibody titers in IVIGs are likely to benefit from treatment with IVIGs. More research combining virological and clinical data is needed to see whether this hypothesis is true.
References


