Abstract

Objective. A follow-up study of musculoskeletal symptoms after Pogosta virus infection.

Methods. Twenty-six patients with earlier serologically confirmed Pogosta disease were examined. Ultrasonography of affected joints was performed in patients who had chronic musculoskeletal symptoms. Serum antibodies against Sindbis virus were determined. The patients were typed for HLA-DR and B27. Efforts were made using the polymerase chain reaction to demonstrate the virus.

Results. Only 50% of the patients were symptomless 2.5 yr after onset of Pogosta disease. Three patients had fibromyalgia, six had occasional arthralgia and two had chronic arthritis.

Conclusions. The epidemiology of Pogosta disease is changing and practitioners should be better aware of it. Pogosta virus infection may lead to chronic musculoskeletal discomfort and arthritis.

Key words: Pogosta disease, Sindbis virus, Chronic arthritis.

Pogosta disease is caused by a Sindbis-related virus [1] that has not been isolated yet. The disease was first observed in Finland, in the province of Northern Karelia, in 1974 and the clinical picture was first described there. Since then there have been several outbreaks (in 1981, 1988, 1991 and 1995) [2]. It has become apparent that Pogosta disease can also occur elsewhere in Finland, including the southwestern part of the country. The disease occurs in late summer with typical symptoms of rash, arthralgia and sometimes fever [2, 3]. The rash usually vanishes in 4 days, but the joint symptoms can last longer [3].

Similar diseases have been reported to occur in Sweden (Ockelbo disease) and in Russia (Karelian fever) [4, 5]. In Ockelbo disease, chronic arthralgias have been described 3–4 yr after the infection [6]. Disease caused by Ross River virus has been reported to be followed by chronic fatigue syndrome lasting up to 3 yr after the infection [7]. The prognosis of Pogosta disease is considered to be good, but so far no long-term follow-up studies have been carried out.

The purpose of our study was to investigate the duration of the joint symptoms in Pogosta disease. Until now, studies of the chronicity of the joint symptoms have been based only on questionnaires. We took advantage of the fact that 2.5 yr earlier there had been an outbreak of Pogosta disease in southwestern Finland. We also wanted to study whether the clinical features of Pogosta disease in southwestern Finland are similar to those in eastern Finland [3].

Materials and methods

We recruited 30 patients with serologically confirmed (presence of Sindbis-specific IgM antibody) Pogosta disease from western Finland. The patients were contacted by mail and they were asked to visit the Rheumatology Clinic of Satalinna Hospital 2.5 yr after the onset of Pogosta disease. Twenty-six patients came to the clinic, and they were all examined by ML. Those having joint symptoms were also examined by a rheumatologist (RL). X-ray pictures were taken and ultrasonography was performed if arthritis was suspected in the clinical investigation. We had the disease records of all 26 patients from 1995. Fifteen of them were women and 11 men. Their mean age was 47 yr (range 10–77). One child was included in the study. Two of the 26 patients had degenerative osteoarthritis before the onset of Pogosta disease, whereas the remaining 24 patients had no previous joint symptoms.

A specimen for serological studies was taken and erythrocyte sedimentation rate, C-reactive protein, haemoglobin, blood leukocytes and rheumatoid factor were assessed for all patients. We obtained a synovial tissue specimen from one patient with chronic arthritis.
Samples
From each patient, 10 ml whole blood and 10 ml blood were taken for serum separation. The serum samples were divided into aliquots that were stored at −135°C until tested. The lymphocytes were collected by centrifugation after Ficoll-Paque gradient separation and were stored as pellets at −135°C until use. The lymphocytes were homogenized with a QIAshredder (Qiagen, Hilden, Germany) and the samples were prepared for extraction of nucleic acids by isolating RNA from the lymphocytes with a RNeasy minikit (Qiagen) and then diluting the isolated RNA to 60 μl with nuclease-free sterile water (Amresco, Solon, OH, USA).

Reverse transcription–polymerase chain reaction
The cDNA was synthesized using the AMV first-strand cDNA synthesis kit for reverse transcription–polymerase chain reaction (RT–PCR) (Boehringer Mannheim, Indianapolis, Indiana, USA). For RT we used the reaction primer KIP 124 [8], and 8 μl RNA isolated from lymphocytes and sera was used as a template. The cDNA generated by the RT described above was amplified by PCR. The total PCR volume was 100 μl and contained 5 mM MgCl₂, 1.25 mM dNTP, 2 units AmpliTag Gold polymerase (Perkin-Elmer, Foster City, CA, USA), 10 mM Tris (pH 8.3), 50 mM KCl and 10 pmol of the primers OCK 1 and OCK 2, as described by Hörling et al. [8]. The primers were synthesized with an Applied Biosystems 391 DNA synthesizer (PCR-MATE) [8].

The samples were amplified in a Perkin-Elmer thermal cycler under the following conditions: 45 cycles of 95°C for 1 min, 53°C for 45 s and 72°C for 30 s. Ten microlitres of the amplified product was analysed by 1.5% agarose gel electrophoresis and visualized by UV fluorescence after staining with ethidium bromide.

Precautions to avoid false-negative and false-positive PCR results.
To analyse the quality of the extracted RNA and to estimate the presence of components inhibiting RT–PCR, β-actin genes were transcribed and amplified. The primers used for transcription have been described by Halminen et al. [9]. The cDNA was synthesized using primers β-ACT 2 and the AMV first-strand cDNA synthesis kit for RT–PCR (Boehringer Mannheim). The β-actin cDNA was amplified as described by Halminen et al. [10] except that the number of PCR cycles was 35 rather than 31.

Special care was taken from the beginning of our studies to avoid contamination of samples with amplicons [11]. Clinical material was handled whenever possible in laminar flow hoods. Extraction of RNA, preparation of cDNA, preparation of PCR and analysis of PCR products were all performed in different rooms. ART Self-Sealing Barrier tips (M/JP, San Diego, CA, USA) were used to pipette the specimens. Negative controls were included in all phases.

HLA typing
HLA-DR typing by PCR amplification was performed as described by Olerup et al. [12]. HLA-B27 typing was carried out by a PCR method described by Välimaa et al. [13].

Results
Thirteen of the 26 patients were symptomless 2.5 yr after the onset of Pogosta disease (Table 1), including one who had probably had meningitis caused by Pogosta virus. Of the remaining 13 patients, three fulfilled the criteria of fibromyalgia. However, they described their muscle and joint pains as rather mild. The two patients with osteoarthritis, one of whom had severe erosive osteoarthritis, complained that Pogosta disease had worsened their joint symptoms.

Six patients had occasional arthralgia with intervening symptomless periods, and they reported that their joint discomfort was decreasing with time.

Arthritis was diagnosed both clinically and with the aid of ultrasonography in two patients, who were both women. One of them had swelling and tenderness in the proximal interphalangeal joints of the hands, and the other in the metatarsophalangeal joints.

The erythrocyte sedimentation rate varied from 5 to 39 mm/h and C-reactive protein from <10 to 25 mg/l; it was normal in 23 patients. One patient was positive for rheumatoid factor (Table 2).

Antibodies of classes IgM and IgG against Sindbis virus were tested from 25 patients. In three patients, highly positive titres of IgM antibodies were still found 2.5 yr after the infection. Two of these patients were symptomless but one suffered from occasional arthralgia. All of the patients had IgG antibody titres varying from 80 to 2560. In 72% of the patients, IgG antibody titres had risen or stayed at the same level.

Table 1. Chronic musculoskeletal symptoms in 26 patients 2.5 yr after onset of Pogosta disease

<table>
<thead>
<tr>
<th>Chronic musculoskeletal symptoms</th>
<th>26 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>13 (50%)</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Occasional arthralgia</td>
<td>6 (23%)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>2 (8%)</td>
</tr>
</tbody>
</table>

Fibers are numbers of patients unless otherwise indicated.

Table 2. Laboratory findings in 26 patients 2.5 yr after onset of Pogosta disease

<table>
<thead>
<tr>
<th>Laboratory findings</th>
<th>26 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid factor</td>
<td>1/25</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>3/26</td>
</tr>
<tr>
<td>ESR, mean (range) (mm/h)</td>
<td>13 (5–13)</td>
</tr>
<tr>
<td>Presence of IgM and IgG antibodies against Sindbis virus</td>
<td></td>
</tr>
<tr>
<td>IgM antibodies</td>
<td>3/25</td>
</tr>
<tr>
<td>IgG antibodies</td>
<td>25/25</td>
</tr>
<tr>
<td>Presence of HLA B27 and DR4</td>
<td>2/21</td>
</tr>
<tr>
<td>DR4</td>
<td>6/22</td>
</tr>
</tbody>
</table>

Figures are numbers of patients/number of patients tested unless otherwise indicated.
Human leukocyte antigen types B27 and DR4 were tested: only two of 21 patients were B27-positive and six of 22 were DR4-positive. All serum specimens and lymphocyte preparations were negative for viral RNA by PCR.

Discussion

The present study was carried out to investigate patients who had had Pogosta disease in southwestern Finland in 1995. It seems that Pogosta disease occurs far away from the traditional Pogosta virus areas, namely the eastern parts of Finland. There was an outbreak of Pogosta disease in 1995, and our study is the first to identify cases of Pogosta virus infection acquired in southwestern Finland. The possibility of Pogosta disease occurring in this new area should be generally noted.

We also wanted to study the time course of musculoskeletal symptoms after Pogosta disease, and were surprised by the high percentage of patients with various chronic sequelae and symptoms still present 2.5 yr after the onset of Pogosta disease. Only 13/26 patients were symptomless, and altogether 11 had chronic musculoskeletal symptoms and findings that may be due to the Pogosta virus infection. In addition to this, in two patients the pain caused by osteoarthritis had worsened after the onset of Pogosta disease. Three patients had fibromyalgia. It is known that several virus infections may lead to a chronic fatigue syndrome, and it has been reported that, after infection with Sindbis-related Ross River virus, 45% of patients complained of persistent tiredness and lethargy [7]. Unfortunately, no proper control material was obtained. However, we feel that the presence of symptoms in 13/26 patients exceeds the prevalence of them in the normal population.

The most interesting cases were those patients who still had chronic arthritis at the time of our study. There have been reports of chronic arthritis after parvovirus B19 virus infection and B19 DNA has been detected in the synovial tissue of such patients [14, 15]. It would also be interesting to see whether the patients who now have occasional arthralgia will have chronic relapsing arthralgia permanently.

Several investigators have postulated that members of the Old World complex of alphaviruses (Ockelbo, chikungunya and Ross River viruses) may persist in humans, since some patients develop persistent arthralgias after acute infection with these viruses [6, 16]. The detection of IgM antibodies against Pogosta virus and also against Ockelbo and Ross River viruses for prolonged periods after acute infection suggests that there is continuous expression of viral antigen [16]. This supports the hypothesis that alphavirus persistence is involved in the development of chronic musculoskeletal symptoms [16]. We have now studied the persistence of Pogosta virus RNA in peripheral blood cells and patients' sera by RT-PCR, but the results were negative. Ockelbo virus RNA has been demonstrated in skin biopsies in acute Ockelbo infection but there are no findings of viral RNA in any clinical human tissues in patients with chronic symptoms [17]. We also tested Pogosta virus RNA from a synovial tissue specimen of the patient with chronic arthritis, but the results were also negative.

Acknowledgements

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References


