Prevalence of Sindbis-related (Pogosta) virus infections in patients with arthritis

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ABSTRACT

Objective. *To determine the role of Pogosta virus as a triggering infection in non-specific arthritis.*

Methods. *Serum samples of 142 patients with acute arthritis were screened for the evidence of Pogosta virus infection. Serological tests for* Chlamydia trachomatis, *salmonella, parvovirus B19, and* Borrelia burgdorferi *were also carried out. As verified later, 78 of the patients had rheumatoid arthritis and 63 seronegative poly- or oligoarthritis, while one had systemic lupus erythematosus.*

Results. *In the early stage of the joint symptoms 4 patients with rheumatoid arthritis, 1 with seronegative polyarthritis and 1 with systemic lupus erythematosus had recent Pogosta virus infection. Four of them had probably had Pogosta disease at the time of the onset of arthritis. In 11 patients with a diagnosis of seronegative arthritis, serological evidence of preceding infection due to salmonella or* Chlamydia trachomatis *was found, strongly suggesting classical reactive arthritis in these cases.*

Conclusions. *Our study suggests that also a Sindbis virus infection may be associated both to an acute joint inflammation as a part of Pogosta disease or chronic arthritis. At present, this possibility still needs further research.*

Introduction

The list of microbes associated with various joint inflammations is long and steadily growing (1). Generally it is thought that viral arthritides are of short duration. However, several studies have blurred this distinction. Arthritis lasting for months has been described, e.g. after parvovirus B19, hepatitis B and C viruses and rubellavirus (2, 3). Pogosta virus has been thus far a less recognised arthritogenic microbe. It is an alphavirus of type arbo A, antigenically closely related to the Sindbis virus and is transmitted by mosquitoes (4). At present several of them are known to cause arthralgia, some of them prolonged cases (5,6). We have seen one case of Pogosta disease in which chronic erosive arthritis developed (7). These findings raised a question regarding how often patients with early arthritis have evidence of recent Pogosta virus infection.

In Finland Pogosta disease has been reported to occur mostly as periodic outbreaks. These have been seen at least in 1981, 1988 and 1995 (13). Patients with clinical symptoms compatible with Pogosta disease were seen in 1974, when serology was not available.

Our special interest was to analyse the role of Pogosta virus in a community-based cohort of 142 patients with early arthritis during the years 1973-1975. The samples were thus collected at the same time when the first notified cases of Pogosta disease were described in Finland. For comparison, antibodies against other arthritogenic microbes were also determined. As a control sera from blood donors obtained from the Finnish Red Cross were used.

Material and methods

Patients

In the period 1973-1975 patients with recent arthritis were referred to the Rheumatism Foundation Hospital in Heinola. The following selection criteria were used: age 16 years or more, swelling of at least one joint, and duration of disease not more than 6 months. Serum samples were taken at the first hospitalization, and at the time 142 samples were available. The diagnoses were confirmed during follow-up (8). The control group consisted of 100 healthy blood donors collected by the Finnish Red Cross in 1994. Such samples were not available from 1974. In general, blood donors in Finland are healthy adults aged from 18 to 65; 51% of them are female and 49% male. The serum samples had been stored over a 20-year period at -20°C.

Antibodies against Pogosta virus, *Borrelia burgdorferi*, salmonella, and *Chlamydia trachomatis* were measured from the control group and from patients with arthritis. Antibodies against parvovirus B19 were measured from patients with arthritis.

Antibodies against Pogosta virus

Serum antibodies of IgM and IgG class against Pogosta (Sindbis) virus were determined by means of an enzyme im-

munoassay (EIA) method according to Calisher *et al.* (4). Briefly, the microtiter plates were coated with semi-purified Sindbis virus antigen (strain AR 339). Serum dilutions (1:40 – 1:2560) were added to the plates and incubated for two hours at 37°C, after which horseradish peroxidase (HRP)-conjugated anti-human IgG or IgM antibodies (at dilutions of 1:12000 and 1:3000, DAKO, Germany) were added. Orthophenylenediamine (OPD) was used as a color substrate and the optical density was measured at 492 um by a Multiskan Analyzer (Eflab OY, Helsinki, Finland). The last dilution which yielded an OD value higher than 2.5 times the OD value of negative controls were considered positive. The sera positive for IgM were tested for rheumatoid factor (RF) by latex agglutination (Rapi-Tex®RF, Dade Behring Marburg GmbH, Germany). If the test was found to be positive, RF was removed by absorption (GullSORB™, Gull Laboratories, Inc, Salt Lake City, Utah, USA) and the antibody titer was retested.

Antibodies against other microbes

For IgG and IgM class antibodies against parvovirus B19 a commercial EIA kit (Biotrin, Sinsheim-Reihen, Germany) was used.

Chlamydia trachomatis-specific IgG antibodies were measured according to Finn *et al.* (9). Serum antibodies of IgM, IgA and IgG class against Salmonella were determined by the EIA method. Phenol/water-extracted lipopolysaccharides (LPSs) of *Salmonella enteriditis* and *Salmonella typhimurium* were used together (pooled LPS EIA) as antigen (10).

EIA was used to determine antibodies against *Borrelia burgdorferi.* The assay was a modification of the method described by Craft *et al.* (1984), using a sonic extract of bacteria (11).

Results

Samples of 99 women and 43 men were included (Table I). The mean age of the patients was 38 years (range 16-76). Of all patients 78 (55%) had rheumatoid arthritis (RA) according to the American College of Rheumatology (ACR) criteria (12), 63 had non-specific seronegative poly- or oligoarthritis, and one patient was later diagnosed as having systemic lupus erythematosus (SLE) (8). At the beginning of the joint symptoms the presence of IgM as well as IgG class antibodies confirmed recent Pogosta virus infection in 6 out of 142 patients. Four of them had RA, one had seronegative polyarthritis and one SLE (Table II). Two were positive for RF and stayed positive after removing the RF by absorption. All of these RA patients were seropositive in the later stage of the disease. Only one patient in the control group had IgM class antibodies against Pogosta virus (Table III). IgG class antibodies indicating a past infection were detected in 20% of arthritis patients and in 25% of patients in the control group. This was an expected finding, because samples of the control patients were collected later, in the year 1994. Two outbreaks had occurred between the years 1973-1994. When the disease journals were analysed it turned out that the symptoms of 4 patients (3 with RA, 1 with polyarthritis) had started in the fall. This was not the case with 2 patients.

One patient with erosive RA had both IgM- and IgG-class antibodies against *Borrelia burgdorferi* indicating a recent infection (Table III). None had IgM class antibodies against parvovirus

Table I. Some characteristics of the patients.

Number of patients	142	
Female/male	99/43	
Mean age (years)	38	(range 16-76)
Diagnosis established at the Rheumatism Foundation Hospital		
Rheumatoid arthritis	78	(55%)
Seronegative poly- or oligoarthritis	63	(44%)
Systemic lupus erythematosus	1	(0.7%)

Table II. Features of 6 patients in whom a positive test for IgM class antibodies showed recent Pogosta virus infection.

Patient No.	Age (years)	Antibodies against Pogosta virus IgM	Antibodies against Pogosta virus IgG	Rheumatoid factor¶	Final diagnosis
1	54	640	160	+	RA*
2	40	320	160	-	SLE**
3	36	160	160	-	RA
4	37	160	80	+	RA
5	31	160	160	-	Polyarthritis
6	39	80	320	-	RA

¶ By latex agglutination; *rheumatoid arthritis; **systemic lupus erythematosus.

Table III. Occurrence of IgM class antibodies in arthritis patients and healthy controls indicating a recent infection.

		Number of patients having antibodies against				
Final diagnosis	No. of patients	Pogosta virus	Parvo virus	*Borrelia burgdorferi*	Salmonella	*Chlamydia* trachomatis[3]
RA	78	4 (5%)	0 (0%)	1 (0.7%)	2 (3%)	5 (6%)
Seronegative arthritis[1]	63	1 (2%)	0 (0%)	0 (0%)	6 (9%)	5 (8%)
SLE	1	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Controls	100	1 (1%)	NT[2]	13 (13%)	4 (4%)	4 (4%)

[1]Poly- or oligoarthritis; [2]not tested.
[3]Regarding *Chlamydia trachomatis* only IgG-class antibodies were measured.

B19. One hundred patients had IgG class antibodies against parvovirus B19 and 13 against *Borrelia burgdorferi* as a marker of an old infection.

We also tested antibodies against salmonella and *Chlamydia trachomatis*. Five patients with RA and 5 with seronegative poly- or oligoarthritis had high levels of IgG class antibodies against *Chlamydia trachomatis* indicating an active infection. In 2 patients with seronegative arthritis clinical signs of chlamydial infection were noted at the beginning of joint symptoms. Two patients with RA and 6 with seronegative poly- or oligoarthritis had antibodies of IgM and IgG and/or IgA class against salmonella indicating a recent infection. Two of the seronegative arthritis patients had had diarrhea before the onset of joint symptoms.

One patient with simultaneous recent salmonella and *Chlamydia trachomatis* infections was noted. Simultaneous infections together with Pogosta virus infection were not detected.

Discussion

Pogosta disease is an interesting example of arthritis caused by a viral infection. It was first noticed in eastern Finland, in 1974. The clinical picture is typical with rash (88%), fever (23%),and joint symptoms (93%) (13). Similar diseases have been reported from central Sweden and the Karelian region, Russia. They are called Ockelbo disease and Karelian fever, respectively (14). Ockelbo disease has been reported to occur in central Sweden between the 60th and 64th parallels, Karelian fever in the Karelian region in Russia, and Pogosta virus had been thought to cause infections only in eastern parts of Finland. However, according to our new results Pogosta virus infection is common throughout Finland (13).

We investigated the IgM and IgG class antibodies against Pogosta virus from patients with arthritis of recent onset, and compared them to the results of the general population. Although these serum samples were old they were of interest, since the first cases considered to be Pogosta disease were noted in 1974. At that time serology was not available.

The possibility that viruses are involved in the pathogenesis of RA has been considered by several investigators. Some viral infections are well known to be capable of inducing a condition resembling RA. Rubella virus is one example of this. Parvovirus B19 infection may be followed by arthropathies that in some cases resemble RA (2). Alphavirus infections are also common causes of arthralgia and arthritis. Chronic arthralgia lasting up to four years has been described after Ockelbo disease (5). Chronic erosive arthritis has been described in one case after Pogosta virus infection (7).

In the present study 6 out of 142 (4%) patients had serologically confirmed recent Pogosta virus infection. The diagnoses of these patients were RA in 4 patients, seronegative polyarthritis in one, and SLE in one as confirmed after a follow-up of several years. In 4 patients (3 with RA, 1 with polyarthritis) the arthritis had started in late summertime when Pogosta disease usually occurs in Finland. Suprisingly, the samples of these 4 Pogosta disease patients were taken in 1973-1974 before the first outbreak of Pogosta disease. The true endemic rate of Pogosta disease is hard to assess due to the variation in different years. Also, the disease is probably underdiagnosed outside the North Karelian region. The prevalence of Pogosta disease in 1974 is not known. In 1981 a total of 300 cases and in 1995 1310 cases were registered by the National Infectious Diseases Register. In Sweden, however, Ockelbo disease had already been described in the 1960s (14).

For the reason that proper control material from 1973-75 was not available, samples collected in 1994 from healthy blood donors were used. The control group is epidemiologically rather similar to the group of arthritis patients. Since the year 1974, outbreaks of Pogosta disease have recurred every 7 years and the year 1995 was an outbreak year. Thus, the serum samples of both control and arthritis patients were collected one year before the outbreak.

Antibodies against salmonella, *Chlamydia trachomatis*, *Borrelia burgdorferi* and parvovirus B19 were also studied. The role of *Borrelia burgdorferi* and parvovirus B19 as triggering infections for arthritis did not seem important in our study. Eight patients had serological evidence of recent salmonella infection and two of them had clinical evidence of this infection (diarrhea) Thus, these cases can be classified as reactive arthritis. In an earlier study antibodies against yersinia were determined in patients belonging to the same program in the Heinola Follow-up Survey of Arthritis. It turned out that 9% of these patients with recent inflammatory joint disease had serological evidence of past yersinia infection (15). Taken together, the Heinola follow-up commenced in 1973, when antibody determinations against *Chlamydia trachomatis* and the EIA method for salmonella antibody determination were not available. Retrospectively antibodies against a number of microbes could be detected and 4 new cases of ReA were found. It is also obvious that some patients had had Pogosta disease, although the relationship of the infection to arthritis could not be established with certainty. The present results, in agreement with earlier findings, suggest that Sindbis (Pogosta) virus infection may be associated with not only acute but also chronic inflammatory joint disease (6, 7). In order to definitely establish this link, further research is needed.

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