Parvovirus infection in early arthritis

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Abstract

Objective

To analyse the subgroup of early arthritis patients with new onset parvovirus infections for details that may help narrow the population tested.

Methods

From their routine patient charts, patient histories and clinical and serological data were obtained for all 130 patients of the Rheumatology division with parvovirus serology performed. 11 patients had acute parvovirus infections, defined by specific IgM antibodies. 95 patients had a previous infection, 16 were never infected, together forming the n=111 control group, and 8 patients had to be excluded.

Results

Most patients with acute parvovirus infection had an acute onset, highly symmetrical polyarthritis of small joints, which was preceded by prodromal symptoms. Positive ANA were frequently found, whereas C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were only mildly elevated. No frank synovitis was found longer than two weeks after disease onset. Most patients were free of symptoms within three months, and no patient in the parvovirus group developed rheumatoid arthritis or a connective tissue disease.

Conclusion

Parvovirus serology may be helpful in patients with acute polyarthritis of very recent onset, and if they give a history of prodromal symptoms, in particular. In most instances, parvovirus arthritis is an acute disease, which is rapidly self-limiting.

Key words

parvovirus, serology, PCR, polyarthritis, early arthritis, anti-nuclear antibodies

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Introduction

In addition to rheumatoid arthritis (RA), the differential diagnosis of new onset symmetrical polyarthritis includes connective tissue diseases and virus infections. Virus arthritis should evidently not be treated with disease-modifying antirheumatic drug (DMARD) therapy. That this issue is important, is also highlighted by the fact that the American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) classification criteria for RA (1) include an additional point for disease persisting over more than six weeks, thus presumably excluding virus infections. On the other hand, occasionally, such infections may be able to trigger RA (2, 3).

Among the arthritogenic virus infections, those with parvovirus B19 are the most common well defined entity in adulthood, when most patients have either had rubella or have been vaccinated against rubella virus (4, 5). Parvovirus infections have been reported to account for two to twelve percent of all new onset disease, thus constituting a minor, but relevant group of patients with early arthritis (6-9).

Testing for parvovirus serology probably is sensible in a specific group of patients, where this information at least provides for relief, if not directly influencing therapeutic decisions. On the other hand, it is probably not of importance for the majority of patients (10-12). While the infection is associated with a fairly typical picture in childhood, including the "slapped face" appearence, adults with parvovirus infections usually do not show typical skin symptoms (9, 13, 14).

Therefore, we grouped all the patients with early arthritis and IgM antibodies to parvovirus in our division, in order to better define the clinical picture and the course of disease. We compared them to all patients for whom parvovirus serology was ordered, but IgM was negative. The results suggest that a subset of symptoms effectively narrow the group of patients for whom parvovirus serology may be a useful test to order.

Patients and methods

We compiled data on all patients for whom parvovirus serology was ordered by the Rheumatology outpatient clinic or the Rheumatology inpatient ward at the University Medical Center. All patients included gave their informed consent to anonymised analysis of their clinical routine data. This approach is in agreement with the German Laws and the Declaration of Helsinki, and was approved by the Ethics Committee of the Clinical Centre and the Medical Faculty. From January 2007 to December 2011, all patients with a serological test for parvovirus B19 infection were evaluated. Patients with pre-existent rheumatic disease or inadequate documentation of clinical data and allocated patients after external diagnosed and successfully treated illness were excluded.

To increase the sample of patients with acute parvovirus B19 infection, one single patient diagnosed after the study period was also included into the sample. The diagnosis of a current parvovirus B19 infection was based on positive specific immunoglobulin M (IgM) and IgG antibodies detected by enzyme immunoassay (Biotrin). For confirmation, parvovirus B 19 DNA was detected from patient serum by real time PCR on a Light Cycler 1.5 instrument (Roche Diagnostics) (15). Primers and probes are directed towards the conserved sequence of the parvovirus B19 major capsid protein VP2.

Information from the rheumatology charts of these patients were retrospectively analysed, collecting data on age, sex, clinical symptoms, laboratory results, auto-antibodies, therapy and disease outcome. The history of prodromal symptoms was taken at time of the first clinical consultation, and before any serological test was performed.

To describe the arthritis, the first swollen and tender joint count by a physician was used. If arthritis was already subsiding at that time, patient history was substituted. As in the ACR-EULAR classification criteria for RA (1), shoulder, elbow, knee and ankle joints were regarded as large joints, and wrists, finger and toe joints as small joints.

Arthritis was supposed to be in remission if the patient was seen symptom-free without any specific medication or if patients stopped consulting the physician because symptoms had ceased.

Disease duration was defined as period from the beginning of arthropathy to the date when the patient was symptom-free. The course of disease was considered chronic if joint symptoms persisted for more than three months.

Statistics

All metric data were tested for Gaussian distribution, using D'Agostino and Pearson omnibus normality tests. If normally distributed, data were described as mean ± standard deviation (SD), and Student's *t*-test was performed for group comparisons. Otherwise, data were represented as median and range and Mann-Whitney tests were used. Categorical data were analysed by Fisher's exact test and χ^2 test for 2x2 and larger tables, respectively. For disease outcomes, Kaplan-Meier curves and log-rank tests were used. For 11 pre-defined comparisons (sex, age, prodromal symptoms, CRP, ESR, small joint involvement, symmetrical joint involvement, remission, positivity for ANA, RF, and anti-CCP antibodies) Bonferroni-corrected *p*-values (p_c) were calculated, and reported in the two cases where that changed significance. All other *p*-values are descriptive only.

Results

Patient sample

In total, 130 patients had parvovirus B19 serology performed. Of these, eight had to be excluded by criteria (defined above). Eleven patients had positive parvovirus B19 specific IgM and IgG antibodies, and thus received a diagnosis of acute parvovirus B19 infection. For eight of the eleven patients, PCR analysis was performed in addition, always confirming parvovirus B19 infection.

With the control group of the other 111 patients, 95 (86%) had IgG, but not IgM anti-B19 antibodies in their sera, as a sign of earlier infection. In one patient, a borderline result for IgM anti-B19 antibodies was found in addition to IgG antibodies, but PCR did not detect any parvovirus B19 DNA. The remaining 16/111 patients were entirely seronegative for parvovirus B19.

Patients were predominantly female in both the parvovirus infection (10/11) and the control group (79/111), (p=0.29). Median age was 45 years (range 21–59 years) for the parvovirus infection group and 45 years (range 18–83 years) for the control group (p=0.81).

Table I. History of and clinical findings in patients with serological evidence of active parvovirus arthritis.

Patient	Age	Sex	Onset	Prodromal symptoms	1st visit (days after onset)	SJC	TJC
1	21	F	May 2010	Respiratory infection	2	0	1
2	43	F	Apr 10	No	3	14	14
3	50	F	May 2007	Flulike symptoms	5	5	7
4	41	M	Sep 11	Respiratory infection	7	24	24
5	54	F	Sep 10	Respiratory infection	14	0	0
6	39	F	Jan 10	Rash, oedema	28	0	0
7	48	F	Nov 10	No	30	0	0
8	46	F	Jan 10	Respiratory infection	38	0	2
9	40	F	May 2014	Rash	42	0	0
10	45	F	Apr 10	Flulike symptoms	44	0	0
11	59	F	Jun 10	Respiratory infection	45	0	0

SJC: swollen joint count; TJC: tender joint count; F: female; M: male.

Final diagnosis of patients in the comparator group

Among the 111 patients with negative IgM antibodies to parvovirus B19, rheumatoid arthritis was finally diagnosed in 19 patients (17%), connective tissue disease in 5 patients (5%), including four patients with systemic lupus erythematosus (SLE). The biggest subgroup (32/111) had an acute, self-limiting arthritis of unknown origin, usually manifesting as oligoarthritis (n=16) or polyarthritis (n=13). A variety of other diagnoses were less frequent. For 33 patients, no evidence for an inflammatory rheumatic disease was found.

Symptoms of viral disease

Of the 11 patients with acute parvovirus B19 infection, nine (82%) reported prodromal symptoms before the onset of arthritis (Table I), as compared to only 22 of the 111 anti-parvovirus B19 IgM negative patients (20%), a significant difference (p<0.0001). Prodromal symptoms included respiratory infection in 5 patients, fever or flulike symptoms and rash in 2 patients each, and oedema in one patient.

Onset and synovitis

Patients with parvovirus arthritis were seen earlier than those from the control group (median 28 [2–45] days *vs.* median 38 [1–4383] days after arthritis onset), suggesting a more acute picture (p=0.0307). Swollen joints were still found in 62 of 111 control group patients at the first visit, but in only 3 of the patients with acute parvovirus B19 infection (Fig. 1A, p=0.11). Whether synovitis had subsided depended on the period from the onset of joint symptoms to the clinical examination. In no single case were joints found swollen longer than two weeks after the onset of parvovirus-associated arthritis. In contrast, even in those 93 patients from the control group who were seen two weeks or later after the onset of arthritis, 51 had swollen joints (p=0.0006).

Pattern of joint involvement

Given the fast resolution of arthritis, information on maximal joint involvement had to be based on patient history. Detailed information was documented for ten patients, while polyarticular involvement was the only information for one patient. For the control group, in three cases, the information on joint involvement was not complete enough to be included.

Most patients with parvovirus B19 infection had polyarticular involvement, while one single patient reported oligoarticular involvement. In the control group 59 (55%) suffered from polyarticular, 41 (38%) from oligoarticular, 6 (6%) from monoarticular involvement, and two patients (2%) had no discernible arthropathy (p=0.14). Small joints predominated in 8/10 (80%) patients with parvovirus B19 infection, as com-

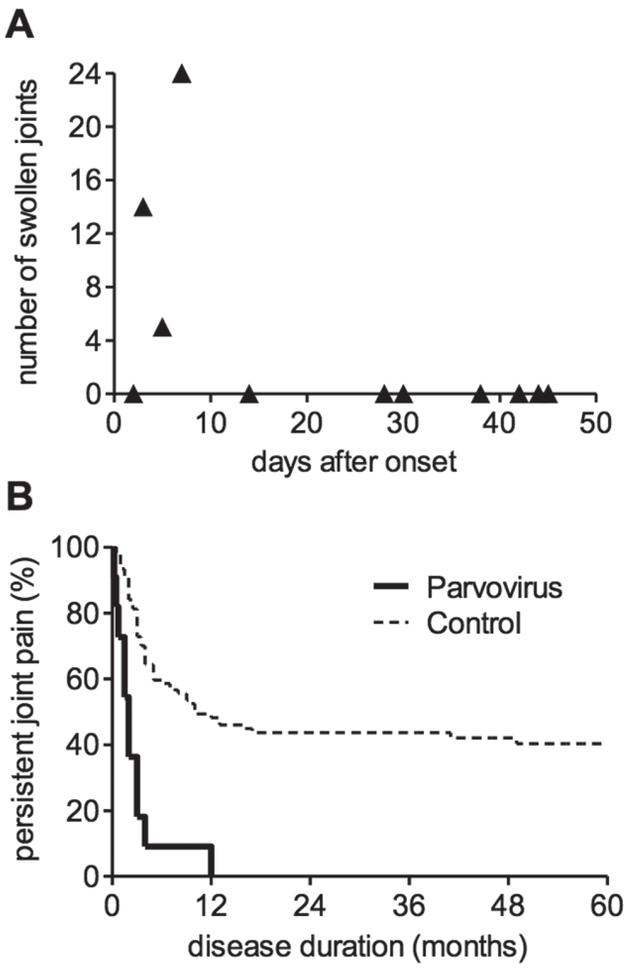

Fig. 1. Disease course in Parvovirus-associated arthritis. Swollen joints were only found early after disease onset (**A**). As compared to the control group (broken, light line), patients with Parvovirus arthritis (heavy line) were free of joint symptoms much earlier (**B**).

pared to 62/106 patients (58%) without new onset parvovirus B19 infection (p=0.31). In patients with parvovirus B19 infection finger joints (9/10) were most frequently affected, followed by knees (7/10), wrists (6/10), ankles (5/10) and toes (5/10), and shoulders (3/10). Parvovirus arthritis was highly symmetrical: of 36 swollen joints of parvovirus patients, 33 (92%) were symmetrically affected, as compared to 206/286 joints (72%) of the control group patients (p=0.0086). This difference would not be significant if corrected for multiple comparisons (p_c=0.0946).

Markers of inflammation

At the first visit, the erythrocyte sedimentation rate (ESR) of parvovirus B19 positive patients did not differ significantly (Fig. 2A, p=0.32), but had a smaller range than in the control group (median 19 [4–42] *vs*. 18 [1–116] mm/h). At the same time, 5/11 patients with parvovirus B19 associated arthritis had a C-reactive protein (CRP) of >5mg/l (Table II), almost identical to 51/111 patients of the control group. The median of CRP values was identical (4.5 mg/l), but, as with ESR, the range was distinctly narrower in parvovirus patients (<1.0–12.3 mg/l) than in the control group (<1.0–329.5 mg/l) (Fig. 2B, p=0.59). CRP tertiles showed no single value of a parvovirus arthritis patient in the highest tertile (>12.5 mg/l), in contrast to 41 values of controls (p=0.0064).

Blood counts and liver function tests

Anaemia was found in 3/11 patients (27%) with parvovirus arthritis vs. 26/111 (23%) without, lymphocytopenia in 4/11 (36%) *vs*. 34/111 (30%), neutrophilia in 2/11 (18%) *vs*. 23/111 (20%), monocytosis in 1/11 (9%) *vs*. 8/111 (7%), and thrombocytosis in 2/11 (18%) *vs*. 10/111 (9%) (p=0.30). Elevated liver enzymes were found in 2/11 parvovirus patients (18%) *vs*. 14/111 (13%) (p=0.64), and increased lactate dehydrogenase (LDH) in 4/11 (36%) *vs*. 15/111 (14%) (p=0.068).

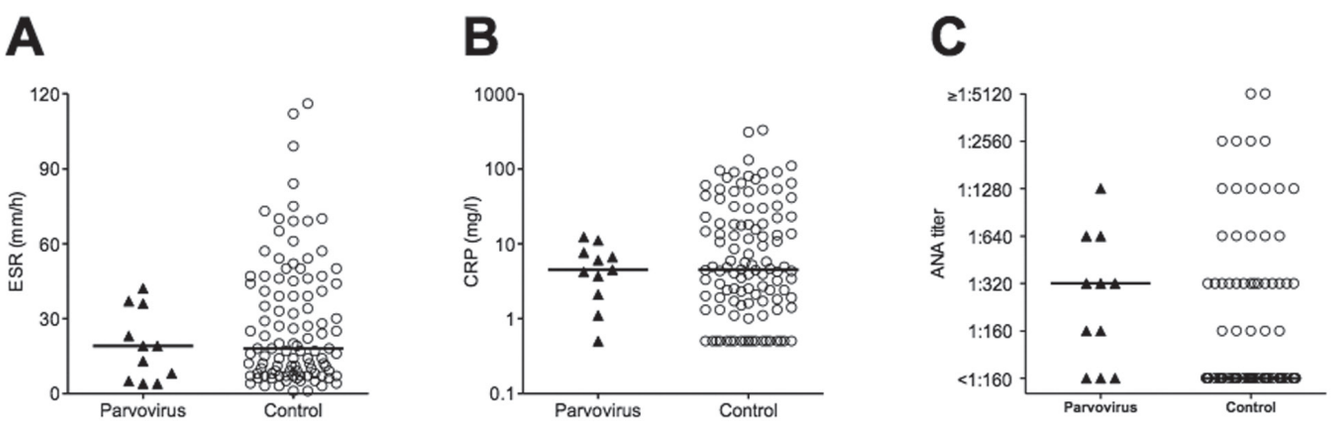

Fig. 2. Serological parameters in patients with Parvovirus-associated arthritis (triangles) and in the control group (circles). Shown are ESR (**A**), CRP (**B**) and ANA (**C**). Since the values were not normally distributed in the control group, the black lines depicted are medians. Non-parametric tests gave p-values of p=0.3227 for ESR, p=0.5909 for CRP, and p=0.0268 for ANA titers.

Table II. Laboratory results of patients with serological evidence of active parvovirus arthritis.

Patient	Parvo IgM	Parvo IgG	Parvo PCR	CRP (mg/l)	ESR (mm/h)	Hb (mmol/l)	WBC (GPt/l)	Plt (GPt/l)	ANA	RF (IU/ml)	antiCCP (U/ml)
1	+	+	+	7.6	36	7.4	6.9	445	1:320	neg	1.93
2	+	+	+	4.5	23	7.6	7.3	323	neg	neg	2.79
3	+	+	+	12.3	37	6.4	3.9	169	1:1280	neg	11.19
4	+	+	ND	11.1	13	8.2	4.4	327	1:640	neg	1.94
5	+	+	+	6.0	4	7.4	8.5	407	1:160	neg	2.22
6	+	+	+	6.6	19	7.9	11.5	281	1:320	neg	2.79
7	+	+	ND	<1.0	8	7.7	8.8	407	neg	30.9	1.48
8	+	+	+	4.2	42	7.3	6.2	399	neg	neg	1.85
9	+	+	ND	1.1	5	8.2	4.4	299	1:320	neg	1.40
10	+	+	+	2.1	19	8.0	4.2	175	1:320	neg	16.07
11	+	+	+	3.7	4	8.7	5.7	277	1:160	neg	1.44

IgM: immunoglobulin M; IgG: immunoglobulin G; PCR: polymerase chain reaction; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; Hb: haemoglobin; WBC: white blood cell; Plt: platelets; ANA: antinuclear antibodies; RF: rheumatoid factor; antiCCP: anti-cyclic citrullinated peptide, + positive; ND: not done, neg negative.

Table III. Findings in this study and in the literature.

Reference	Number of cases	Prodromal symptoms	RF positive	ANA positive	Symptoms >6 weeks	Reported fully resolved
This study	11	9/11	1/11	8/11	6/11	11/11
(9)	19	13/19	1/19	0/19	17/19	NR
(14)	37	20/27	1/26	0/17	2/24	22/24
(18)	7	NR	0/7	0/7	5/7	4/7
(31)	20	NR	1/12	NR	12/20	11/20
(21)	9	1/9	1/9	1/9	3/9	7/9
(22)	5	1/5	2/3	0/1	0/5	5/5
(32)	9	NR	0/2	0/2	2/9	9/9
(23)	16	NR	3/8	2/8	3/12	10/12
(24)	9	4/9	0/9	4/9	9/9	6/9
Together	142	48/80	10/106	15/83	59/125	85/106

RF: rheumatoid factor; ANA: antinuclear antibodies; NR: not reported.

Autoantibodies

All patients with parvovirus B19 infection were tested for rheumatoid factors (RF) and anti- cyclic citrullinated peptides antibodies (anti-CCP) antibodies, finding only one single patient with a positive RF and no patient with positive anti-CCP antibodies (Table II). In the comparator group, 13 of 108 tested were positive for RF (p=1.00) and 7/102 positive for anti-CCP antibodies (p=1.00).

In contrast to the RA antibodies, antinuclear antibodies (ANA) were frequently positive in patients with parvovirus B19 infection. Of the eleven patients, eight had ANA ranging in titer from 1:160 to 1:1280 on immunofluorescence (Fig. 2C). Fine granular fluorescence was seen in five of these samples, granular, nuclear and fine granular plus nuclear in one each. In the control group, the majority of patients (67/103) patients were ANA negative (p=0.0214, p_c=0.2354). Titers in the 36 ANA positive samples ranged from 1:160 to >1:5120 (p=0.0268).

7 of the parvovirus B19 positive patients were tested for anti-neutrophil cytoplasmatic antibodies (ANCA), all with negative results.

Therapy and course of disease

Of the 11 patients with parvovirus B19 associated arthritis, 8 received nonsteroidal anti-inflammatory drugs (NSAIDs), and 2 were additionally treated with prednisolone. No patient required a DMARD during the follow-up period. Of the 111 patients in the control group, 81 received NSAIDs, 54 prednisolone, 31 conventional DMARDs, 5 biological DMARDs, and 15 antibiotics.

In all parvovirus B19 positive patients disease was self-limiting with complete clinical remission, whereas 47 (44%) of the 107 patients, for whom follow-up information was available, went on to chronic persistent arthritis (p=0.0031).

Among patients with disease resolution, 9/11 patients (82%) with parvovirus B19 arthritis were free of symptoms within 3 months, in contrast to only 31/60 patients (52%) in the comparator group. The significantly different courses of disease are depicted in Fig. 1B (p<0.0001).

Discussion

In this study, we analysed all patients tested for parvovirus B19 serology as outpatients or inpatients of the Rheumatology division. Although formally done at the discretion of the treating physician, essentially all of these testes were ordered in the context of early arthritis. In the patient group tested, 9% had evidence of active parvovirus infection, which is the range found in other reports on early arthritis (8,9), while Harrison *et al*. (6) reported a lower frequency of only 2.7%.

As expected (2, 16), patients with parvovirus infection were predominantly middle-aged women with a symmetrical polyarticular involvement that almost always included the small joints of the hands. In fact, only one single patient in the parvovirus group had suffered from oligoarticular involvement. The affected joints of parvovirus patients quite strictly followed a symmetrical pattern (92%).

The fact, that eight of the eleven patients had no palpable synovitis any more at their first visit restricted our ability to securely differentiate between

arthritis and arthralgia. However, the same finding strongly supports another conclusion: Our data imply an acute onset of arthritis and a rapidly self-limiting course of parvovirus arthritis, *i.e*. patients were seen rapidly after the onset because of the patients' acute complaints, but, given the appointment system in place, often not fast enough to still capture overt arthritis. In contrast to the control group, the only patients with palpable synovitis were seen within two weeks of the onset of joint symptoms. No single parvovirus patient had swollen joints after this time-point, suggesting that the arthritis usually resolved within two weeks.

In our study, all parvovirus B19 infected patients were free of any symptoms at their last clinical visit, and four out of five were symptom-free within 3 months. No patient developed rheumatoid arthritis or a connective tissue disease. Whereas joint symptoms have been reported to resolve within a few weeks without joint destruction (17), Woolf *et al*. (18) found that the arthropathy lasted more than 2 months in one of five patients. Some groups, and White *et al*. in particular (9), reported more persistent problems (Table III). In terms of chronic progression Gran *et al*. (19) reported one patient developing RA, SLE, and unclassifiable connective tissue disease, each.

More frequently than in other studies (Table III), the treating physicians had documented a patient history of prodromal symptoms of virus disease (7/11) or rash (2/11) before the onset of arthritis. In a series of 27 patients, Reid *et al*. (14) reported prodromal symptoms in 20 patients, of whom 13 had a parvovirus rash. Other groups had even lower rates of patients with prodromal symptoms (Table III). That information may predispose such patients to be tested for parvovirus, and it is unclear whether this is due to factual differences or to history taking and documentation. However, such prodromal symptoms are an argument for parvovirus serology in very recent onset polyarthritis. This would have limited testing to 31 patients in our cohort, of whom 9 had a new onset parvovirus infection.

Findings in routine laboratory diagnosis after acute parvovirus B19 infection came to no surprise (3, 20, 21). Blood counts were abnormal, elevated liver enzymes and LDH were found in some cases, but neither differentiated parvovirus patients from the control group. Markers of inflammation were not different between the groups either. In the majority of cases, normal ESR and CRP were found, well in line with other reports (9, 14, 19, 22-25). While the absence of high acute phase parameters was not a significant argument for parvovirus infection, very high acute phase parameters would argue against this diagnosis.

Parvovirus B19 has been shown associated with auto-antibodies, RF and ANA in particular (4, 5, 26-28). Occasionally, this may herald RA or SLE, potentially triggered by parvovirus infection (2, 25, 29, 30). Much more commonly, however, such antibodies will be a transient phenomenon. In line with the published literature, only approximately one in ten patients with parvovirus arthritis will have positive RF (Table III). In some contrast, we found positive ANA, ranging in titer from 1:160 to 1:1280, in eight of eleven patients. This is considerably higher than in the majority of published reports (Table III), which together would suggest ANA to be only marginally more common than RF. In fact, only Nesher *et al*., in a series of lupus-like cases (31), published comparable results, with 12 of 14 patients ANA positive. In our series, there was no indication of a connective tissue disease in any patient.

This study is limited by the relatively small number of cases and by its retrospective character. However, it represents the full spectrum of patients tested for parvovirus infection in a real life Rheumatology setting.

In conclusion, we aimed at finding parameters that limit parvovirus serology to a group of patients with higher likelihood. Indeed, prodromal symptoms, an acute onset of a symmetrical polyarthritis and very recent onset have turned out to be arguments for ordering parvovirus serology. A positive result may provide relief to the patient, given the usually benign course, and potentially prevent risks of unnecessary treatment. Our data also support the connotation of the ACR/EULAR criteria for RA (1) that six weeks of persistence of palpable synovitis are sufficient to make virus arthritis very unlikely.

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