Chronic Parvovirus B19 Infection Resulting in Chronic Fatigue Syndrome: Case History and Review

S. Kim Jacobson, Jennifer S. Daly, Grace M. Thorne, and Kenneth McIntosh

From the Division of Infectious Diseases, Department of Pediatrics, Harvard Medical School, Boston; Children’s Hospital, Boston; and The Medical Center of Central Massachusetts, Worcester, Massachusetts

The spectrum of disease caused by parvovirus B19 has been expanding in recent years because of improved and more sensitive methods of detection. There is evidence to suggest that chronic infection occurs in patients who are not detectably immunosuppressed. We report the case of a young woman with recurrent fever and a syndrome indistinguishable from chronic fatigue syndrome. After extensive investigation, we found persistent parvovirus B19 viremia, which was detectable by polymerase chain reaction (PCR) despite the presence of IgM and IgG antibodies to parvovirus B19. Testing of samples from this patient suggested that in some low viremic states parvovirus B19 DNA is detectable by nested PCR in plasma but not in serum. The patient’s fever resolved with the administration of intravenous immunoglobulin.

The chronic fatigue syndrome continues to challenge the medical profession with regard to both etiology and management. In general, there is little in the way of specific treatment, although infrequently a causative agent may be identified and specific therapy may be available. Parvovirus B19 was first described in 1975 [1], and since then the spectrum of disease caused by this virus has continued to grow. We present the case of a young woman who experienced an illness indistinguishable from chronic fatigue syndrome, who also had a high and persistent fever and was shown to have chronic parvovirus B19 infection.

Case Report

An 18-year-old woman seen in August 1994 complained of fatigue of ~10 days’ duration and peripheral asymmetrical joint pain of acute onset. Initial empirical treatment was with oral tetracycline for presumptive Lyme disease. Doxycycline was substituted after the patient developed gastrointestinal upset. One week after the onset of symptoms, she developed a lacy maculopapular rash, predominantly over her arms, which lasted a few days.

At that time her complete blood cell count was unremarkable, apart from mild leukopenia (leukocytes, $4.4 \times 10^9/L$). She also had a mildly elevated anti-streptolysin O titer of 288 IU (normal, <200 IU). Over the ensuing weeks, she experienced continuing fatigue and joint pain, accompanied by morning stiffness. In October she was seen again by her physician because of fevers, which were independently and well documented (maximum oral temperature, 103°F).

She had no rigors but had developed headaches, aphthous oral ulceration, intermittent diarrhea, and significant weight loss (20 lb). At this time a peripheral blood smear showed eosinophilia and 5%–7% atypical lymphocytosis. Serologies for hepatitis B, hepatitis C, and parainfluenza were negative, as was a urine culture.

She continued to have intermittent fevers and abdominal pain. In November she was hospitalized and investigations to exclude inflammatory bowel disease were performed, which revealed lactose intolerance. Her abdominal symptoms resolved with elimination of milk and milk products from her diet. Her fevers, joint discomfort, fatigue, and lethargy continued.

CT scans of her head, abdomen, and pelvis were normal. Cytomegalovirus and Epstein-Barr virus serologies were negative, and the results of thyroid function tests and sedimentation rates were normal, but serological tests for parvovirus B19 revealed IgM and IgG antibodies to parvovirus B19, indicating recent infection (table 1). Lyme disease serology was equivocal, but results were negative when testing was repeated.

It was assumed that the patient would gradually recover, but she continued to have symptoms, and in January 1995 she returned with complaints of disabling lethargy and fatigue, headaches, and irregular fevers. Because of her disability, she deferred starting college and was forced to curtail her physical activities. At this time, tests were performed for detection of HIV antibody, rheumatoid factor, antinuclear antibodies, and...
Table 1. Serological and PCR results for a young woman who had fevers, joint discomfort, fatigue, and lethargy.

<table>
<thead>
<tr>
<th>Testing date</th>
<th>IgM</th>
<th>IgG</th>
<th>Serum</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>November 1994</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>January 1995</td>
<td>–</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>March 1995</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>–</td>
</tr>
<tr>
<td>May 1995</td>
<td>ND</td>
<td>ND</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>June 1995</td>
<td>ND</td>
<td>ND</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

NOTE. ND = not done; + = positive; – = negative.

Complement, but the results of these tests were normal; in addition, serology for Bartonella henselae, Bartonella quintana, and Bartonella elizabethae was negative. She was mildly anemic, with a hematocrit of 35.1%.

Her symptoms remained essentially unchanged over the next several months, and she underwent intensive investigations. A rapid plasma reagin card test; determinations of ferritin, vitamin B12, folate, and liver enzyme values; blood cultures; tests for dsDNA antibodies; EIA for C4, C3, SS-A/Ro, and SS-B/La antibodies; and MRI of the brain were performed, none of which were contributory to a diagnosis. Her headaches and fevers became so disabling that naproxen and fluoxetine, and then nortriptyline, were prescribed. Her symptoms diminished but did not resolve.

In March parvovirus serology was repeated and she still had IgM and IgG antibodies to parvovirus B19. At this time parvovirus B19 DNA was first sought in her serum by PCR and was found to be present (figure 1). She had a marginally depressed IgA level but otherwise normal quantities of immunoglobulins and IgG subclasses. HIV serology was repeated and was again negative.

There was little resolution in her symptomatology, and in May PCR for parvovirus B19 was repeated on both serum and plasma. At this time her plasma was PCR-positive but her serum was PCR-negative (figure 2). A decision was made to treat her with intravenous immunoglobulin, and 3 weeks later PCR on her plasma for parvovirus B19 was negative. After treatment, her condition began to improve, and during follow-up for a further year, she completely recovered.

Methods

DNA was extracted from the patient’s serum and plasma by proteinase K digestion, phenol/chloroform extraction, and ethanol precipitation [2]. The extracted DNA was then amplified by a nested technique [3] with two sets of primers (Genosys Biotechnologies, The Woodlands, TX): p1 (1399–1422) and p2 (1498–1525) and p5 (1600–1576), resulting in a 202-bp product, and p6 (1682–1659), resulting in a 102-bp product. This product corresponds to a genetic sequence within the nonstructural gene NS-1.

The product was detected by ethidium bromide staining after electrophoresis on 2% agarose gels. All specimens were run in duplicate and with positive and negative controls to control for reproducibility and contamination. IgM and IgG antibodies to parvovirus B19 were detected by ELISA with use of a cloned complete structural protein (VP-1) as the antigen (SmithKline, Van Nuys, CA). This method has a sensitivity of at least 90% and a specificity of >98% and is similar to other parvovirus B19 ELISAs reported on elsewhere [4].
Discussion

Chronic Fatigue Syndrome

The patient fits very well into the revised classification for chronic fatigue syndrome (CFS) [5]; debilitating fatigue and multisystem symptoms of at least 6 months’ duration, often starting with a flu-like illness, and characterized by fever, myalgias, malaise, respiratory tract symptoms, and sometimes gastrointestinal symptoms). This syndrome was first described in the time of Hippocrates and has been the subject of much speculation throughout ancient and modern times.

It is likely that there is more than one etiology. Many different microbiological causes of CFS have been postulated, including Epstein-Barr virus, cytomegalovirus, human herpesviruses 6 and 7, enteroviruses, retroviruses, and Borrelia burgdorferi, and research supporting and refuting these theories has been published [6–15]. In addition, many researchers believe that there may be some underlying immunological abnormality in association with viral infection that results in this syndrome [16–19].

The syndrome of fibromyalgia has features in common with CFS, and patients presenting with this syndrome have been shown to have evidence of recent infection with parvovirus B19 [20]. However, a study exploring the incidence of parvovirus B19 infection in patients whose conditions met the case definition of CFS did not show an association with this virus [21].

Our patient underwent extensive investigations because of her persistent and high fever (temperatures as high as 103°F). Durack and Street [22] proposed the definition of classic fever of unknown origin (FUO) as fever present during 3 days of hospital investigation or over three outpatient visits that does not have an obvious cause; our patient’s condition fits this definition as well as that for CFS. There is some overlap in the clinical manifestations of CFS and FUO, and it is important to exclude all possible infectious causes for both syndromes.

Clinical Manifestations of Parvovirus B19 Infection

Parvovirus B19, first described in 1975 [1], has been associated with a number of well-documented clinical syndromes. Although infection may be subclinical, it is the cause of erythema infectiosum, or “slapped-cheek syndrome,” in childhood. In adults, especially females, parvovirus B19 infection may result in peripheral symmetrical arthralgia and arthropathy.

Parvovirus B19 infection is known to cause hematologic abnormalities in susceptible hosts, including anemia, thrombocytopenia, leukopenia, and aplastic crisis. Other, less common manifestations have been reported such as systemic necrotizing vasculitis, neurological abnormalities, pneumonia, myocarditis, hepatitis, and pseudoappendicitis [23–25], and it is likely that the full range of symptoms is yet to be described.

The virus is notoriously difficult to culture, and clinical syndromes may occur some time after the acute infection because of the development of antibody responses. Consequently, patients may no longer have IgM antibodies to parvovirus B19 on investigation. Patients who are immunocompromised may have persistent symptoms, especially chronic anemia, which may be associated with prolonged viremia [20, 23].

Parvovirus B19 is one of the family Parvoviridae, which also includes the genera dependoviruses and densoviruses. Dependoviruses require coinfection with adenoviruses in order to infect the host, and although no known symptoms are caused by these viruses, they are known to result in latent or chronic infection [26]. It is possible that under certain circumstances, possibly genetically determined, parvovirus B19 (a close relative) may cause chronic or latent infection and therefore reactivation, even in those who are not detectably immunosuppressed.

Recent research has demonstrated the ability of this virus to cause chronic infection in the bone marrow of patients with chronic B19 arthropathy [27], and persistent viremia has been shown to occur in asymptomatic patients [28, 29]. In addition, a study to determine the clearance of parvovirus B19 after acute infection showed that 13 of the 14 patients studied were viremic 2–6 months after infection and 1 of the 14 was positive by nested PCR for 1 year after infection [30].

For most patients the diagnosis of parvovirus B19 infection has been made serologically, by the detection of IgM and/or IgG antibodies to parvovirus B19. Antibody may not be detected, however, in patients who are chronically viremic. Such patients continue to have measurable virus, without detectable IgG antibody [28, 30]. In view of these problems, it seems prudent to exclude chronic/persistent viremia in patients who present as our patient did.

PCR has been a very useful technique [3], and it may be with the advent of PCR that more accurate detection of infection, particularly chronic infection, will be possible. We have noticed that when there is a low level of viremia, only the nested PCR product is detectable and is often found in plasma but not in serum [authors’ unpublished data]. In contrast, when there is a high level of viremia, the unnested product can often be detected and is found equally in serum and plasma. The reasons for this are unclear; however, there are two possible explanations.

First, this finding may be a result of the complexing of small concentrations of the virus in fibrin clots, as was postulated by Coombs et al. [31] when they noticed the same phenomenon in HIV PCR. Second, the concentration of the virus may be so low that even though controls are not inhibited by serum PCR inhibitors, there may be enough inhibition to prevent detection of very tiny amounts of virus. These possibilities are illustrated in our case; toward the end of our patient’s illness, we were able to detect the parvovirus B19 DNA nested product only in her plasma, not in her serum.

Conclusions

We have presented the case of a young woman with chronic fatigue, headache, and a fever who had chronic parvovirus...
B19 infection and whose condition improved clinically after intravenous immunoglobulin therapy. We have shown that we detected parvovirus B19 DNA initially in serum and plasma but later in plasma only. We suggest that parvovirus B19 chronic/persistent viremia should be excluded for some patients who present with symptoms compatible with CFS or FUO, even if antibodies to parvovirus B19 are present.

In addition, the suitability of serum vs. plasma for PCR diagnosis of parvovirus B19 infection should be investigated. Further study of the length of time patients are viremic after infection is also called for, in order to confirm reports of prolonged viremia and to recognize patients in whom the virus may in fact be chronically present.

References