Meningoencephalitis with Persistent Parvovirus B19 Infection in an Apparently Healthy Woman

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A case of meningoencephalitis, associated with persistent parvovirus B19 infection, is described in a 36-year-old immunocompetent woman. Parvovirus B19 DNA was detected in samples of cerebrospinal fluid and serum; no parvovirus B19–specific clinical symptoms were seen, but neurological episodes were observed in the presence of parvovirus B19 infection and despite the onset of a specific immune response.

A previously healthy, immunocompetent 36-year-old woman presented to her provincial hospital in late May 2006 with high-grade fever (≥38°C), headache, left-hand paraesthesia, neck stiffness, and chest pain. Cardiological examination results and chest radiography findings were negative; empirical antibiotic treatment with clarithromycin was administered, and the patient was discharged from the hospital. In spite of the treatment, the symptoms deteriorated further, and the patient was admitted to the same hospital 5 days after being discharged.

At admission, the patient was fully oriented, with clear consciousness. She experienced pain and stiffness in her neck, headache, and a progressive paraesthesia involving the whole left side; she did not have lymphadenopathy or rash.

Results of bacteriological examinations of blood and CSF specimens and pharyngeal swabs were negative. Laboratory examinations of the CSF specimen showed a high pleocytosis (WBC count, 370 cells/μL [normal WBC count, <5 cells/μL]; neutrophil:lymphocyte ratio, 90%:10%), an increased protein level (0.93 g/dL [normal protein level, 0.2–0.4 g/dL]), and a normal glucose level (0.55 g/dL [normal glucose level, 0.50–0.60 g/dL]). Serological tests excluded active infection by enterobacteria, Mycoplasma, hepatitis B virus, HIV, hepatitis C virus, human cytomegalovirus, Epstein-Barr virus, and herpes simplex virus 1/2. Abnormalities in the brain were detected using electroencephalogram and CT. MRI demonstrated a high-intensity signal of periventricular white matter and 2 punctuate areas of enhancement in the corpus callosum in both T1- and T2-weighted scans.

Results of clinical and laboratory examinations were consistent with a pattern of viral meningoencephalitis. The patient was treated with dexamethasone (16 mg per day) for several days; she gradually recovered over 6 days, and her neurological state improved to normal. Shortly thereafter, the patient developed type 2 diabetes mellitus; therefore, dexamethasone treatment was gradually removed, which led to the reappearance of neck stiffness and paraesthesia on the left side.

Steroid therapy was resumed with dexamethasone (4 mg per day) for a week, followed by methylprednisolone (16 mg per day) that was tapered off 3 weeks later. Again, when the steroid treatment decreased, the neck stiffness reoccurred. Treatment with methylprednisolone (16 mg per day) was maintained.

Because the symptoms persisted, the patient was moved to the regional hospital. At that time (August 2006), the patient was still experiencing headache, left-side paraesthesia, and intermittent pyrexia. MRI demonstrated the same abnormalities in the periventricular white matter that had been observed previously. Examination of a CSF specimen showed a slightly increased WBC count (11 cells/μL) and normal levels of proteins (0.25 g/dL) and glucose (0.51 g/dL). Isoelectrofocusing tests of the CSF specimen revealed oligoclonal bands in the third basic zone, which indicated an intrathecal synthesis of total IgG. Acute infections due to hepatitis B virus, hepatitis C virus, HIV, adenovirus, cytomegalovirus, herpes simplex virus 1/2, human herpesvirus 6, varicella zoster virus, enterovirus, Mycoplasma, Coxiella burnetii, Toxoplasma, Entamoeba histolytica, Echinococcus granulosus, Aspergillus, Cryptococcus, Treponema pallidum, and Borrelia burgdorferi were excluded by serum antibody analysis. Tests for additional viruses were performed, and evidence of an acute parvovirus B19 infection was found. High levels of parvovirus B19 DNA were detected in serum (1.83 × 10^4 IU/mL) and in CSF (2.69 × 10^7 IU/mL) specimens using a calibrated real-time PCR assay [1]. Parvovirus B19–specific ELISA (EIA Biotron) results were positive for IgM and negative for IgG. Parvovirus B19–specific IgM and IgG were undetectable in the CSF specimen. The time course of parvovirus B19 virological and serological analyses, starting...
with the time when the first serum sample was available (August 2006), is reported in figure 1.

At the time of diagnosis of parvovirus B19 infection, the patient reported that her 5-year-old son had presented a “slapped cheek” rash and that her husband had complained of a self-limiting flu-like illness 10 days before her first hospitalization. Parvovirus B19 infection was confirmed in her son and her husband by the detection of parvovirus B19–specific IgM in serum samples.

The diagnosis of parvovirus B19 infection was consistent with the anemia of the patient. In particular, during the period from June through August 2006, her hemoglobin levels fluctuated between 7.9 and 10.9 g/dL. Laboratory examinations of peripheral blood samples did not detect hemoglobin variants or hemoglobinopathies. Because parvovirus B19 DNA was detected in serum samples, the anemia was finally associated with parvovirus B19 infection and was treated in late August 2006 with transfusions of concentrated RBCs (2 units). The patient was also treated with commercially available intravenous immunoglobulin (Ig VENA N. I. V.; Kedrion) at a dosage of 20 g per day for 5 days. After blood transfusions and immunoglobulin therapy, her hemoglobin level increased, and a decrease in peripheral blood viral load was observed (from $4.20 \times 10^4$ IU/mL to $9.23 \times 10^3$ IU/mL). The patient reported an initial, gradual improvement in symptoms, but shortly thereafter, she experienced intermittent pain in her cervical/dorsal rachis, myalgia of legs, and thorax neuropathy. These neuropathic symptoms were more marked at night and were treated with pregabalin.

In October 2006, because neurological symptoms persisted,
serological and virological tests were repeated. B19 DNA was still present in serum samples at a low level, even in the presence of parvovirus B19–specific antibodies. An additional 5 days of intravenous immunoglobulin therapy was given in an attempt to clear the virus from the patient; serum and CSF specimens were obtained after the treatment to assess the results. A low level of parvovirus B19 DNA was found in the serum sample but was undetectable in the CSF specimen.

In December 2006, the patient partially recovered; she reported only transient episodes of headache, and hematological parameters revealed a moderate anemia that did not require blood transfusions. Nine months after the initial diagnosis of parvovirus B19 infection and 11 months after the onset of symptoms, parvovirus B19 was not detected in the patient’s blood.

The present report describes a case of long-term parvovirus infection characterized by meningoencephalitis, neurological sequelae, and anemia in an apparently immunologically healthy woman. Generally, in an immunocompetent host, parvovirus B19 infection can be asymptomatic and is usually overcome by the development of a neutralizing immune response. Symptomatic infection is commonly associated with numerous acute diseases, such as erythema infectious (fifth disease), postinfection arthropathies, transient aplastic crisis (in patients with hemolytic disorders), and foetal hydrops [2]. Improvements with regard to the development of immunological and molecular virological diagnostic methods have shown that the spectrum of B19 diseases is broader than previously considered. In addition to the typical features, parvovirus B19 has been implicated in a wide spectrum of illness, including hepatitis, myocarditis, chronic fatigue syndrome, carpal tunnel syndrome [3], recurrent erythema [4], and dermatological and neurological presentations [5]. Increasingly, parvovirus B19 is recognized as potentially playing a role in the pathogenesis of some neurological disease, such as encephalitis, aseptic meningitis, and meningoencephalitis [6]. Barah et al. [7] estimated that the incidence of undiagnosed meningoencephalitis that can be attributed to parvovirus B19 infection during an outbreak year in the United Kingdom was 4.3%. Moreover, Hobbs [8] recently published data to support that at least 14% of the human population has parvovirus B19 DNA detectable in the brain. As these authors aptly point out, parvovirus B19 may more commonly infect and persist in the human brain than was previously thought.

The mechanism by which parvovirus B19 affects the CNS is not clear. However, the detection of the parvovirus B19 genome and the expression of viral protein were previously demonstrated in cells of macrophage/microglia lineage and in endothelial cells of cerebral white matter, respectively. Thus, parvovirus B19 can infect and possibly replicate in human brain cells [9]. In spite of this, several groups [10] have proposed that neurological manifestations could be mainly related to an inappropriate immune response, rather than direct viral toxicity.

The case described depicts a several-month history of recurrent parvovirus B19–associated neuropathies in an apparently immunologically healthy woman; parvovirus B19 DNA was detected for several months despite the presence of high titers of anti–parvovirus B19 IgM and IgG antibodies. No typical parvovirus B19–related symptoms were observed, such as rash, arthralgia, and postinfection arthropathies (the most common manifestations of a long-term parvovirus B19 infection in women). The diagnosis of parvovirus B19 infection was consistent with the neurological symptoms and hematological data. However, the anemia was not promptly recognized as a diagnostic marker of parvovirus B19 infection, and the role of parvovirus B19 in the persistent meningoencephalitis was established 2 months after the onset of clinical symptoms with the detection of high levels of parvovirus B19 DNA in both serum and CSF samples. Parvovirus B19 was cleared from the patient and the patient’s neurological syndrome was cured with immunoglobulin therapy.

In conclusion, our data clearly demonstrate that the possibility of parvovirus B19 infection should be investigated for patients with neurological symptoms in the absence of any parvovirus B19–specific clinical symptoms and regardless of immune status. Our data also suggest that the full spectrum of parvovirus B19–associated disease is yet to be understood.

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References