Neurological impairment and arthritis in an immunocompetent child with human parvovirus B19 chronic infection

Disturbi neurologici e artrite in un paziente immunocompetente con infezione cronica da parvovirus B19

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INTRODUCTION

Since its discovery, human parvovirus B19 (HPV-B19) infection has been linked with a broad spectrum of clinical diseases in children and young adults [1-3]. Asymptomatic infection is common in children and adults. The best recognized condition related to HPV-B19 is erythema infectiosum (fifth disease) [3]. Joint symptoms are rare in children and become more frequent in adults. Approximately eight percent of children infected with the virus have arthralgia, which symmetrically affects ankles, knees and small joints of the hands [1, 3]. Neurological manifestations in HPV-B19 infection are less common, but are currently receiving increasing attention: neurological disorders, such as encephalitis, meningitis, brachial plexus neuropathy and Guillain-Barré syndrome have been recently associated with HPV-B19 [4-12]. Persistent HPV-B19 infections have been usually described in children with various congenital or acquired immunodeficiencies [3, 12]. Studies in such patients and in the general population have convincingly shown that the humoral immune response plays a well-documented role in both the clearing of acute HPV-B19 infection and in the prevention of re-infection [13, 14]. In this case report, we describe an immunocompetent child with evidence of persistent HPV-B19 infection, arthritis and neurological impairment.

CASE REPORT

An eight-year-old Caucasian male was referred to our hospital in July 2006 for fever, headache and arthritis at wrists and ankles. No significant anamnestic data were reported. Upon admission there were a fine maculopapular rash of the groin area and arthritis at both wrists and ankles. No neurological signs were present at the onset. No other signs or symptoms were reported. Serological examination showed high C-reactive protein (CRP) of 13.4 mg/dl (normal values below 0.5) and an erythrocyte sedimentation rate (ESR) of 29 mm/h (normal value below 20 mm/h). Haemoglobin value and platelet count were normal, and biochemical examination was unremarkable. HPV-B19 DNA was detected in serum by polymerase chain reaction (PCR). Anti-HPV-B19 IgM and IgG antibodies were positive. On the contrary, PCR for Human Herpes Virus 6, Cytomegalovirus and Epstein-Barr Virus were negative in serum. Our patient was treated with non-steroidal anti-inflammatory drugs and discharged after one week in good clinical condition, with no rash and no arthralgia.
went magnetic resonance, which showed increased signal intensity at the spinal roots in the lumbar region, compatible with polyradiculoneuritis (Figure 1).

Electrodiagnostic studies (somatosensory evoked potential) were negative. A five-day treatment with intravenous immunoglobulin (400 mg/kg/day) for the persistence of HPV-B19 infection produced a good clinical response, with an improvement in muscular tone and in walking, and no reported side effects. Hence he was discharged after ten days with no therapy.

When he returned three weeks later for a check-up, he had normal reflexes and neither arthritis nor myalgia. He underwent magnetic resonance, which was normal, and PCR for HPV-B19, that was negative in serum and in plasma. Laboratory analyses were unchanged. He underwent his last clinical control in January 2008 and was still in good clinical condition.

**DISCUSSION**

HPV-B19 is usually a self-limiting infection: in immunocompetent children, the symptoms normally last a few weeks and become persistent or recurrent only in a minority of patients [2, 3]. Our patient presented with an unusual onset of the disease and developed an atypical clinical course, due to a probably prolonged state of viral persistence.

In the literature, chronic HPV-B19 infection is described mainly in immunodepressed patients, unable to mount an adequate neutralizing antibody response and to clear the virus [3, 12-14]. Few patients have been described as being affected by a prolonged illness without clinical or laboratory evidence of underlying immunodeficiency [1, 3].

Our patient did not suffer from diseases related to impaired T-cell function, showed a normal immune response to other infections and had a normal immunoglobulin level, excluding general B-cell dysfunctions. That said, despite the development and the presence of HPV-B19 specific immune reaction, he showed a prolonged state of viraemia and was incapable of clearing the HPV-B19 infection. Therefore, the defect in immunity associated with the establishment of persistent HPV-B19 infection may be subtle.

This could be due to an inadequate immune reaction against the viral capsid proteins VP1 and

Six months later, the patient started referring several episodes of headache, sporadically followed by vomiting. In February 2007, after two months, he was admitted to our hospital for his persistent headache and for weakness, arthralgia, myalgia and tremors in his legs and hands. Upon clinical examination he could not walk unaided and he had arthritis in both ankles. Muscle tone had generally decreased; bilateral patellar and Achilles reflexes were weak, and the Lasegue sign was positive.

Serological examination showed a normal complete blood count, low CRP (0.36 mg/dl) and high ESR (67 mm/h). Haemoglobin value was normal and biochemical examination was unremarkable.

Anti nuclear antibody was negative. The humoral immune response was normal as well as the T- and B-cell subsets. The PCR for HPV-B19 DNA was positive both in serum and plasma. Anti-HPV-B19 IgM antibody was negative and IgG positive. To exclude other infections, we performed PCR and specific antibody dosage for Borrelia, Yersinia, Campylobacter, Chlamydia, Cytomegalovirus and Epstein-Barr Virus, all negative.

Cerebrospinal fluid examination showed normal protein concentration (22 mg/dl) and 2 leukocytes per millilitre. Moreover, it was negative for HPV-B19 DNA by PCR, as well as for Borrelia, Yersinia, Campylobacter, Chlamydia, Cytomegalovirus, and Epstein-Barr Virus.

The patient started the therapy with non-steroidal anti-inflammatory drugs with improvement in his arthritis but with persistence of difficulty in walking and myalgia. He under-
VP2, which have been shown to contain epitopes that induce the production of B19-neutralizing antibodies.

Another possibility is that the inability to eliminate HPV-B19 might be associated with decreased antibody affinity [15, 16].

Persistent HPV-B19 infection usually manifests as chronic anaemia in immunodepressed hosts. Generally, these patients do not suffer from skin rash or arthralgias [3, 12]. By contrast, our patient had a normal haemoglobin level and presented at the onset with arthralgias and skin rash.

Moreover, he developed neurological symptoms, including weakness, myalgia, tremors in his legs and hands and an inability to walk unaided.

We detected no HPV-B19 DNA in his cerebrospinal fluid. We think that the association between neurological impairment and serological examination is strongly suggestive of HPV-B19 related chronic infection. Indeed, anti-HPV-B19 antibody and HPV-B19 DNA have been demonstrated to be highly effective in establishing diagnosis in immunocompetent children [13, 17].

Moreover, a negative cerebrospinal fluid examination was also found in 19% of patients with neurological manifestations associated with HPV-B19, as described in a previous study of Douvroyiannis et al. [10]. In this case, the pathogenic mechanism of neurological impairment is supposed to be immunomediated, as postulated by other authors [8, 9]. In particular, neurological manifestation coincided with symptoms of arthritis and with the appearance of specific HPV-B19 IgG antibodies, suggesting immune complex deposition.

There is no specific antiviral drug against HPV-B19 infection, but a number of alternative options to eliminate the virus can be recommended, including anti-inflammatory drugs and intravenous immunoglobulin [14].

According to most studies, treatment of persistent HPV-B19 infection with intravenous immunoglobulin may improve patient status or cure the disease [18-19].

As in other cases of chronic HPV-B19 infection, our patient had a good clinical response after intravenous immunoglobulin therapy, with the resolution of neurological symptoms. Magnetic resonance demonstrated increased signal intensity at the spinal roots in the lumbar region, compatible with polyradiculoneuritis. A few weeks after immunoglobulin therapy, the patient underwent a second magnetic resonance, which was negative.

The excellent response of radiological findings to therapy of HPV-B19 infection with intravenous immunoglobulin can be assumed as further evidence for the aetiopathogenetic relationship between HPV-B19 and neurological disease.

Key words: human parvovirus B19, neurological impairment, arthritis, children.
REFERENCES