Unusual association of diseases/symptoms

IVIg treatment for VZV-related acute inflammatory polyneuropathy in a child

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Summary

Acute inflammatory polyneuropathy is an inflammatory demyelinating disease triggered by an autoimmune mechanism. It follows an infection or an immunisation after a free interval of 2–30 days. We report a case of a 14-year-old boy who develops an acute rapidly progressive paraplegia, urine incontinence and positive Lasegue a week after a characteristic chickenpox rash. Spinal MRI showed diffuse thickening and leptomeningeal enhancement of cauda equina nerve roots. Intravenous immunoglobulins were given and yielded a dramatic clinical and radiological improvement. The patient was discharged without any clinical problems 1 month after the onset of symptoms. We performed a review of the literature, discussing the different forms of varicella-zoster virus-related central and peripheral nervous system complications and management strategies for acute postinfectious encephalomyelitis/radiculitis.

BACKGROUND

Acute inflammatory radiculitis is an acute immune-mediated inflammatory disorder with multifocal demyelisation, affecting the central nervous system (CNS) and peripheral nervous system (PNS). It may occur days or weeks after febrile illness, immunisation, exanthema (measles, rubella, smallpox and chickenpox), or respiratory infection by Epstein-Barr virus, Cytomegalovirus, *Mycoplasma pneumoniae*.¹

CASE PRESENTATION

A Caucasian 14-year-old boy presented with headache, positive Lasegue and lower-limb functional impotence. Tactile and proprioceptive sensations of the lower limbs were preserved, but nociceptive one was impaired. He came from an urban area, with no personal and family history note.

Eight days before the beginning of neurological symptoms, a generalised, polymorphic rash developed diagnosed as chickenpox by the general practitioner. Varicella-zoster virus (VZV) immunisation had not been performed.

Skin examination at the time of admission to our hospital revealed the presence of only crusty lesions. During hospitalisation, serial neurological examinations and laboratory studies showed rapidly deteriorating paraplegia, voiding difficulty with urine retention. Motor nerve and sensory conduction studies showed abnormal conduction patterns of both peripheral motor and sensory roots of lower limbs. Atonic bladder was confirmed by urodynamic study. Cognitive functions, cranial nerve examinations and cerebellar tests were unremarkable.

INVESTIGATIONS

Cerebrospinal fluid (CSF) studies showed: glucose 71 g/dl, proteins 88 g/dl, 21 cells/ml³. Anti-VZV (IgG and IgM), VZV and herpes simplex virus (HSV) PCR, viral and bacterial CSF cultures resulted negative as well as CSF oligoclonal bands and angiotensin I-converting enzyme.

VZV serology was compatible with acute infection (positive IgM and negative IgG) and confirmed clinical suspect. C-reactive protein level, white-cell and platelet

count were in the range of normality. Blood tests were negative for antinuclear antibody, anticardiolipin antibodies, anti-SSA, anti-SSB, rheumatoid factor and antidouble-stranded-DNA antibody. Levels of IgA, IgG, IgM, IgE, C3 and C4 were normal. HIV test was negative.

Chest x-ray and brain MRI revealed no pathological findings. Spinal MRI showed diffuse thickening and leptomeningeal enhancement of cauda equina nerve roots (figure 1A).

DIFFERENTIAL DIAGNOSIS

Infectious polyradiculitis must be excluded before concluding to an acute form of postinfectious inflammatory polyradiculitis. For this reason, patients' CSF should systematically be screened for herpes infections (HSV and VZV), viruses relevant to specific geographical regions and other frequent causes of infectious CNS/PNS disorders. Brain malignancies, including CNS lymphomas, should also be considered. Many systemic diseases (Behcet's disease, systemic lupus erythematosus and sarcoidosis), primary or secondary small-vessel CNS vasculitis, vascular, toxic or infectious leucoencephalopathies (bacterial and tuberculous meningitis, VZV encephalitis, HIV localisations, neurosyphilis, Lyme disease and cerebral malaria) can mimic inflammatory polyradiculopathy, as well as acute and chronic inflammatory demyelinating polyradiculoneuropathy (AIDP/CIDP).²

TREATMENT

In our case, large spectrum antibiotics and intravenous acyclovir were performed with no improvement. After microbiological results (negative CSF cultures, negative VZV and HSV PCR) in the suspect of a postinfectious inflammatory polyradiculitis, intravenous immunoglobuline (IVIg) therapy (2/kg/daily of for 5 days) was administered.

OUTCOME AND FOLLOW-UP

The patient had a progressive and complete normalisation of clinical findings. MRI performed after 1 month showed the radiological resolution of the condition (figure 1B).

Figure 1 Sagittal MR T1-weighted images after intravenous gadolinium injection at the onset of symptoms (A) and after 30 days of therapy (B). All the inflamed cauda equina nerve roots and adjacent leptomeninges are thickened and show marked enhancement (arrows in (A)). After 1 month (B) the pathological enhancement was clearly decreased.

At 1 year of follow-up the boy was in a good clinical status, without voiding difficulty or neurological sequel.

DISCUSSION

The neurological complications of VZV infections (eg, acute cerebellar ataxia, AIDP and AIDP variants, myelitis and radiculitis, optic neuritis, meningitis and encephalitis and vasculopathy) can be categorised into those caused by the primary infection and those that are associated with an immunomediated inflammation triggered by the infection.

The first forms are characterised by the presence of VZV DNA or anti-VZV IgG or both in CSF.³ Several patients respond to antiviral therapy.⁴⁻⁶ The benefit of steroid administration in addition to antiviral agents is still unknown,⁷ since they can promote further viral replication and progressive damage.

The second forms can be distinguished from acute viral infections because the disease is not the result of primary tissue invasion by the infectious organism (therefore no virus can be isolated by CSF tests). These forms are thought to be immune mediated and are characterised by perivenular inflammation and demyelination. The lesions are located around small vessels in the cerebral white matter, brainstem, spinal cord and nerve roots and are composed of lymphocytes and mononuclear cells. Grey matter may also be involved, particularly basal ganglia, thalami and brainstem. The involvement of the immune system is thought to imply the molecular mimicry phenomenon, consisting in structural homology between a

pathogen and myelin proteins of the host leading to T-cell activation and specific autoimmune CNS/PNS response.²

In our case, a polyradiculitis due to direct viral infection could be a hypothesis, but the negative microbiological tests (cultures and PCR), the lack of response to acyclovir therapy and the interval between initial VZV infection (chickenpox) and the development of neurological symptoms are considered as the immune-mediated VZV infection-related acute inflammatory polyneuropathy as a stronger diagnosis.

Acute inflammatory polyneuropathies account for about 7% of all complications of varicella. However, in all patients with varicella, it is a rare complication (8 of 2534 patients in one study). There are no characteristic features to distinguish this postvaricella polyradiculopathy from any other acute inflammatory polyneuropathies that follow other infections. Acute inflammatory polyneuropathies with cranial nerve involvement (extraocular nerve paralysis with diplopia, facial diplegia and bulbar involvement) have been reported, but it was not the case of our patient.⁸

There is no standard treatment for immune-mediated VZV-related neurological complications, since there have been no studies which have directly compared IVIG with steroids, plasma exchange or other immunomodulatory treatments. High-dose intravenous steroids are widely accepted as first-line therapy; nevertheless, but high-dose steroid treatment is not without risk: hyperglycaemia, hypokalaemia, high blood pressure, mood disorders and growth retardation should be carefully monitored.⁹

Moreover, a wrong diagnosis and an unnecessary steroid treatment may promote viral replication and lead to rapid progression and deterioration of clinical status.

For these reasons, there have been recent advances in the use of high-dose IVIG in a number of autoimmune disorders that has led to its application to immune-mediated neurological disorders, such as postinfectious encephalomyelitis, myasthenia gravis, acute and chronic inflammatory demyelinating polyneuropathies and multiple sclerosis.^{10–12} Published case series advocate doses of 1–2/kg, administered over 3–5 days.¹³

Postulated mechanisms of IVIG in immunomediated diseases include the binding of immunoglobulin to Fc receptors on macrophages,¹⁴ anti-idiotypic antibodies in the infused immunoglobulin, feedback inhibition of antibody production, direct effects on antibody binding sites on nerves,¹⁵ non-specific effects on natural killer cells and increased activity of non-specific T-suppressor cells.¹⁶

Two reports on the effective role of IVIG postinfectious encephalomyelitis have already been described in the late 1990s.^{17–18} Both male patients (8 and 11 years of age) quickly recovered after IVIG therapy. Other three children aged 2–5 years with suspect postinfectious encephalomyelitis rapidly improved after treatment with IVIG.¹⁹

In 2006, Mariotti *et al*²⁰ treated a child with relapsing VZV-related postinfectious encephalitis with IVIG for 5 days, with improvement of ataxia, dysarthria and weakness.

Recently, a 31-year-old lady with herpes virus 2-related postinfectious encephalomyelitis had only partial clinical response to intravenous dexamethasone, but a dramatic clinical improvement to IVIG,¹ as well as two patients described by Sahlas *et al* in 2000.²¹

Owing to recent literature and potential side effects of steroid therapy, we decided to treat our patient with IVIG, obtaining a complete resolution of clinical symptoms and radiological findings. We suggest that IVIG should be considered for the treatment of paediatric patients with inflammatory conditions of the PNS.

Learning points

- ▶ The present paper was aimed to alert paediatricians about the possible development of extremely uncommon, chickenpox-related complications.
- ▶ Varicella-zoster virus (VZV) involvement should be considered in the differential diagnosis of the cauda equina syndrome.
- ▶ There are only few reports on the management of this rare complication of VZV infection. According to our experience, intravenous immunoglobulins represent an effective and safe treatment for inflammatory conditions of the peripheral nervous system in children.

Competing interests None.

Patient consent Obtained.

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