

Neurological Complications of Varicella-zoster Virus Infection

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The varicella zoster virus is the etiologic agent of varicella and shingles. It is a virus known to infect the nerve tissue and can cause persistent infection by quartering to the dorsal nerve, cranial nerve and autonomous roots. The most common complication is bacterial superinfection of skin lesions, but in terms of severity and sequelae, neurological complications are very important. Neurological complications of varicella-zoster infection are rare and consist of aseptic meningitis, myelitis, encephalitis, cerebellar ataxia, Reye's syndrome, Guillain Barre syndrome, optic neuritis, vasculitis, ventriculitis, post-herpetic neuralgia. A fairly significant rate of neurological phenomena post VZV infection appear in the absence of the characteristic rash. Therefore, the clinician must have a high degree of suspicion regarding this possible viral etiology of acute neurological events and routine testing for the virus (especially, viral DNA by PCR from CSF) are advised. Therapeutic options are fairly limited and sequelae may develop.

Keywords: central nervous system, encephalitis, meningitis, myelitis, diagnosis, treatment

Varicella-zoster virus (VZV), belonging to the alpha-herpesviruses family, has a genome of double stranded DNA and has nervous tissue tropism. After the initial acute infection – varicella, it has the ability to cause persistent infection, being located in the dorsal nerve root, cranial nerve and autonomous nodes. Its reactivation is associated with a decrease in cell-mediated immunity (age/immunosuppression) [1].

The most common complications of varicella-zoster virus infection are: bacterial superinfection of skin lesions, transient hepatitis (up to 50% of children with chickenpox), varicella-associated pneumonia, thrombocytopenia. Neurological complications are rare. These include: encephalitis and cerebellar ataxia, Reye's syndrome, Guillain Barre syndrome, optic neuritis, vasculitis, post-herpetic neuralgia [2].

The detection of VZV DNA in the CSF by PCR and VZV antibodies are diagnostic methods with great sensitivity. CSF cytology and biochemistry may help establish the correct diagnosis [3].

The treatment of these complications is based on the classic antiviral acyclovir that could be associated with corticosteroids. There is controversy in this regard, given the uncertainty over the etiopathology of these events – immunological, infectious, postinfectious).

The prognosis of neurological complications is favorable in children and good in adults, but long-term studies to quantify the sequelae of these complications are insufficient [1].

Neurological complications of varicella-zoster virus infection occur after both chickenpox and shingles (apparently more frequently after shingles). There have been reported cases where they occur before the rash, or in its absence. They affect both the central and the peripheral nervous systems.

The incidence of neurological complications in children after chickenpox is 0.5-1.5 / 1000 (the most common are the cerebellitis and encephalitis). In adults, 15% of patients with herpes zoster develops post-herpetic neuralgia.

Neurological complications chicken pox (0.01-0.03% of patients) are represented by: aseptic meningitis, myelitis, encephalitis, cerebellar ataxia, Reye's syndrome, Guillain Barre syndrome, optic neuritis, vasculitis, ventriculitis [1].

Neurological complications of infection's reactivation include: post-herpetic neuralgia, meningitis, encephalitis, myelitis, optic neuritis, retrobulbar neuritis, cranial nerve palsy, focal motor deficits, neurological bladder, Guillain-Barre syndrome.

It is noted that several studies show a fairly significant rate of neurological phenomena post VZV infection in the absence of characteristic skin manifestations. Therefore, a high degree of suspicion is necessary regarding possible viral etiology of these events and routine testing for this virus too (viral DNA by PCR from the CSF) (4).

Cerebellitis - acute cerebellar ataxia

Is the most common neurological complication in children (median age of 3 - 5.5 years), with an incidence of 1 per 4,000 cases.

The onset is acute, typically within one week of developing the rash and can last for 2 to 4 weeks. The events may occur sometimes even with 3 days before the appearance of skin lesions and more than 3 weeks after [5].

From the clinical point of view, we find: unsteady gait, broad-based, nystagmus, slurred speech, dysmetria, weakness, headache, tremor, mild neck stiffness.

It was initially considered a complication of immunological nature, but there were reports that viral DNA was identified in CSF [6,7].

CSF examination is usually normal, but in 25% of cases there may be pleocytosis and increased albumin level.

It usually heals without sequelae, but sometimes cerebellar deficits, hearing impairment or behavior changes can remain [1, 8, 9].

Meningoencephalitis

Is one of the most severe and common neurological complications in VZV infection. In a study conducted in Switzerland in 2003-2010, in 519 patients (over 16 years)

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diagnosed with encephalitis, only 2.1% were confirmed with VZV infection (PCR viral DNA in CSF) [10].

It represents the second leading cause of viral meningitis after enteroviruses and the third of viral encephalitis, after enteroviruses and herpes simplex virus [24]. It appears in 0.1-0.2% of patients with VZV infection.

Patients present with headache, fever, altered consciousness, seizures, mental disorders, signs of focus [8].

Mortality among hospitalized adults was estimated at 9-20%. Survivors may have sequelae with varying intensity, which may include: intellectual and memory deficits, personality or motor changes who shall not heal for the next 10 years [11]. In children the incidence was estimated at 0.2 cases per 100,000 children, and the average age of occurrence is 5.4-6.4 years.

The viral DNA was identified in small and large vessels of anterior and posterior cerebral circulation and not in the grey matter of the brain, suggesting that encephalitis is caused by a vasculopathy and not by direct damage of the brain substance [12].

Vasculopathy associated with VZV infection

The vascular damage of CNS is caused by the presence of the virus in blood vessels and the endothelial damage and subsequent thrombus formation causes strokes or transient ischemic attacks (TIA). Other pathological events that can occur are: infarction in the spine, brain aneurysms or subarachnoid or intracerebral hemorrhage.

MRI and CT craniocerebral highlights ischemic or hemorrhagic changes [8].

Unifocal vasculopathy associated with VZV infection

Affect immunocompetent patients with advanced age and has sudden onset.

It acts as a focal deficiency that occurs in weeks-months after the reactivation of varicella zoster virus infection in the contralateral trigeminal nerve. It may present as an acute stroke.

Typically occurs seven weeks after the onset of the zoster rash, but may occur even after 6 months. In 20-25% of cases neurological sequelae will develop.

The pain may be self-limited or progressive, with mortality of up to 25%.

Angiography reveals narrowing and obstruction of the middle or anterior cerebral artery. Retinal artery occlusion may occur [8].

Multifocal vasculopathy associated with VZV infection

It occurs more often in immunocompromised patients (cancer, HIV, transplant). It can also occur in the absence of a rash.

The onset is subacute and the patient will have hemiplegia, aphasia, visual field deficit, focal deficits or fever, headache, altered consciousness, vomiting, seizures.

CSF examination reveals mononuclear pleocytosis and slight increase albuminorahiei. VZV DNA and IgG VZV are positive from the CSF.

MRI examination reveals multiple craniocerebral ischemic or hemorrhagic infarcts in subcortical and cortical area in the white and grey matter [8,13-15].

Paralysis of cranial nerves

The most frequently involved is the trigeminal nerve with its branches: the optic nerve, the maxillary nerve and the mandibular nerve.

Also, reactivation of infection in cranial nerve VII (zoster oticus or Ramsey-Hunt syndrome) is manifested by peripheral facial palsy and rash on external ear canal and even on the eardrum. It may be accompanied by dizziness, headache, tinnitus, hearing loss [8].

Myelitis

Is generally an uncommon complication of infection with varicella-zoster virus, which occurs more frequently in immunocompromised host, with an incidence of less than 1: 1000 cases.

The pathophysiologic mechanism it hasn't been elucidated yet, but several hypotheses have been issued: neuronal or glial direct infection, vasculitis, ischemic necrosis, autoimmune demyelination.

The symptoms may appear days to weeks after the onset of the rash and is manifested by paralysis of extremities, difficulty in bladder and intestinal motility, as well as lack of sensitivity dissociated or segmental. The clinical prognosis can be excellent but a severe evolution has been reported. Transverse myelitis, Brown-Sequard syndrome or ascending myelitis also may occur.

CSF examination identifies pleocytosis and increased proteins and VZV-DNA, anti-VZV antibodies are positive [1,8].

Reye syndrome

Implies the presence of encephalopathy and liver failure, that is associated with varicella and consumption of acetylsalicylic acid [8].

Optic nerve damage

VZV infection can cause retinal necrosis or progressive outer retinal necrosis (PORN). Most cases occur in immunocompromised patients (CD4 counts below 10 cells / mm³) and may be associated with meningo-encephalitis or vasculopathy. Ganciclovir treatment has better results compared to acyclovir [8].

Post-herpetic neuralgia

Post-herpetic neuralgia is the most common complication of shingles, with a frequency of approximately 10% and due to the intensity, duration and therapeutic difficulties it is sometimes a challenge [1,8].

Acute post-herpetic neuralgia is defined as pain rush until 30 days after the onset of symptoms and chronic post-herpetic neuralgia is characterized by pain that persists longer than 4 months after the onset of skin symptoms.

In most cases, the rash of herpes zoster is preceded by a prodrome manifested by pain and paresthesia, at that dermatome.

Allodynia (pain caused by non painful stimuli typically touch) is typically present in acute shingles.

It is more common in older people and manifests as pain, burning, itching in the region where the rash was present. Secondary post-herpetic neuralgia disorders are insomnia, anorexia, weight loss, weakness, fatigue, depression.

Risk factors that predispose to the occurrence post-herpetic neuralgia are: older age, female sex, the presence of the prodrome, severity of rash [16,17].

Laboratory diagnostic

Recently it has been shown that many of the neurological complications of VZV infection can occur in the absence of specific exanthema or other clinical symptoms that suggest this etiology. This makes very important to use a more complex investigation algorithm (that preferably includes molecular biology methods) for these patients.

Often, CSF microscopic examination shows a moderate pleocytosis (<100 ECN / mm³) with lymphocytic predominance, an increased level of albumin (altered blood-brain barrier). Oligoclonal bands may be present, and total IgG levels may be elevated in CSF.

Anti VZV antibody levels in the CSF are helpful in the diagnosis of neurological complications of VZV infection. The amount of viral DNA after developing symptoms gradually decrease to disappear after 1-3 weeks of illness [19]. Quantitative determination of viral load in the CSF could be a tool to assess response to antiviral therapy in these patients [20].

Determination of intrathecal IgG antibodies and their correlation with plasma levels can be useful in cases where testing was performed later in the course of the disease (when the viral DNA is absent). However, the presence of antibodies in the absence of viral DNA (identified by PCR) is not always suggestive for the diagnosis, and may be a consequence of vaccination or a primo-infection.

Imaging techniques (MRI, craniocerebral CT) can reveal ischemic or hemorrhagic changes (rarely). Pathological changes are located deep in the gray or white matter. Angiography reveal the presence of focal/ segmental narrowing on the affected arteries. In case of myelitis, spinal MRI reveals hyper T2 to the affected area.

Electronic microscopy of the biopsy preparations reveals inflammation of the arteries with multinucleated giant cells, Cowdry type A inclusions, viral fragments [21]. CSF virus isolation or detection by immunofluorescence are diagnostic methods that are increasingly less used.

Treatment

Extensive therapeutic trials are missing, possibly due to the low incidence of these manifestations of VZV infection. Acyclovir is used to treat herpes infections for many years and has a good activity to VZV, but due to low penetrability in the brain, high-dose and parenteral administration is preferred. A careful assessment of comorbidities and renal function are preferable, especially in elderly patients.

Valaciclovir, due to an increased bioavailability after oral administration could be an alternative.

In focal vasculopathy, myelitis and acute cerebellar ataxia associated with VZV infection acyclovir is recommended at 10mg/kg/8 h for 7 days. The treatment duration in immunocompromised patients will be longer - 10 to 14 zile. Cortisone therapy (prednisone 60-80 mg/day for 3-5 days) should be associated to reduce inflammation in the CNS. In small vessel vasculitis the intravenous aciclovir role is less clear. Anecdotally, satisfactory results were obtained.

In Ramsay Hunt syndrome prednisone 1 mg / kg / day for 5 days in tapering dose and acyclovir (250mgx3 / day IV or 800mgx 5/day orally) is also recommended.

In post-herpetic neuralgia acyclovir po / iv and tricyclic antidepressants or gabapentin may be used as a first line treatment. A lidocaine patch 5% may be associated [22].

Conclusions

The clinical spectrum of neurological complications of varicella-zoster virus infection is large and associated with both first infection and reactivation of latent virus. Their occurrence in the absence of the characteristic rash make the etiologic diagnosis sometimes difficult in the absence of virologic and immunological assays. The treatment of acute forms is still based on acyclovir in high doses and parenteral administration, and the evolution, although it is favorable in the majority of cases, can be marked by the apparition of neuro-psychical sequelae.

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