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Neurological complications of varicella-zoster virus infection in children

Powikłania neurologiczne zakażenia wirusem ospy wietrznej i półpaśca u dzieci

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Abstract

Varicella-zoster virus is an exclusively human α-herpesvirus, known as the aetiological factor of chickenpox which is usually linked with childhood. The disease occurs with a worldwide geographic distribution, and in temperate climates shows a seasonal pattern with epidemics occurring mostly during late winter and spring. The annual incidence is estimated at 80–90 million cases worldwide. Children usually acquire varicella during the first five to 10 years of life, and the highest risk of infection is related to household contacts without a history of vaccination. Although the disease is commonly considered benign, varicella-zoster virus bears the potential of causing a wide range of complications, including the most serious ones of central nervous system manifestations. The neuropathogenesis of varicella-zoster virus infections is not well understood. Based on a wide spectrum of clinical syndromes, multiple theories explaining the pathways of spread of the virus, and host immune response to the viral presence have been proposed, including direct retrograde trafficking of the virus and haematogenous spread as well as inflammatory response with vasculitis. Neurological complications related to varicella-zoster virus infection are the second most common indication for hospitalisation in immunocompetent children with varicella, following skin superinfections. In this paper, the neurological aspects of chickenpox in children are discussed. The characteristics of the clinical syndromes, pathogenesis, methods of diagnosis and treatment, as well as long-term consequences are presented.

Keywords: complication, children, childhood, chickenpox, shingles

Streszczenie

Wirus ospy wietrznej i półpaśca – α-herpeswirus – jest patogenem wyłącznie ludzkim, odpowiedzialnym za wywołanie ospy wietrznej należącej do grupy chorób zakaźnych wieku dziecięcego. Choroba występuje na całym świecie, a w klimacie umiarkowanym notuje się jej sezonowość z epidemiami notowanymi głównie w okresie późnej zimy i wiosny. Roczną zachorowalność na świecie szacuje się na 80–90 milionów przypadków. Zwykle dzieci zarażają się ospą wietrzną w ciągu pierwszych pięciu do dziesięciu lat życia, a największe ryzyko zakażenia wiąże się z kontaktami domowymi osób bez wcześniejszej historii szczepień przeciwko wirusowi. Chociaż choroba ta w powszechnej świadomości uważana jest za łagodną, jej przebieg może być powikłamy szeregiem komplikacji, spośród których potencjalnie najcięższe są manifestacje w obrębie ośrodkowego układu nerwowego. Neuropatogeneza zakażeń nie jest dobrze poznana. W oparciu o szerokie spektrum zespołów klinicznych zaproponowano kilka teorii szerzenia się zakażenia oraz reakcji organizmu. Obejmują one między innymi bezpośredni wsteczny transport wirusa drogą nerwów, krwiopochodne rozprzestrzenianie się wirusa oraz odpowiedź zapalną z obecnością zapalenia naczyń. Powikłania neurologiczne związane z zakażeniem wirusem ospy wietrznej i półpaśca są drugim, po nadkażeniach skóry, najczęstszym wskazaniem do hospitalizacji immunokompetentnych dzieci z tym rozpoznaniem. W pracy zaprezentowano powikłania neurologiczne związane z zakażeniem wirusem ospy wietrznej i półpaśca. Przedstawiono charakterystykę zespołów klinicznych, patogenezę, metody diagnozowania i leczenia, a także konsekwencje odległe.

Słowa kluczowe: powikłania, dzieci, wiek dziecięcy, ospa wietrzna, półpasiec

INTRODUCTION

Varicella-zoster virus (VZV) is an omnipresent, human causative pathogen of primary varicella, often called chickenpox, and its reactivated form of herpes zoster (HZ) referred to as shingles.

The name of the virus itself and of the diseases it causes have interesting historical connotations. In French, the name "varicella" was used to describe an exanthem caused by the disease that was thought to be a benign form of the malignant variola. In English-speaking countries, varicella has been usually called "chickenpox," probably to describe more pictorially the size of the vesicular lesions, being similar to a chickpea (from the French, *pois chiche*) (Greenthal, 1926). The term "zoster" was used for describing the dermatomal exanthem, as the typical location of the disease corresponded well to the position of the characteristic belt (zoster) worn by Greek warriors to secure their armour. Similarly, "shingles" is the anglicisation of the French word *chingle*, meaning a belt.

The first records of vesicular rashes associated with chickenpox and shingles as we know them today come from ancient times. However, it was not until 1888 that a relationship between HZ and chickenpox was suggested (Bokay, 1909). Establishing this link represented one of the significant hurdles in the history of VZV research. In the absence of an animal model, most of the evidence needed to be obtained by clinical and epidemiological observations. The von Bokay hypothesis found its substantiation in the early 1950s, when the virus was isolated from both chickenpox and zoster, and compared (Weller, 1953).

Neurological complications in the form of encephalitis and cerebellitis during primary and reactivated disease were recognised since the beginning of the 20th century. Still, it was not until 1966 that VZV was isolated from the cerebrospinal fluid (CSF) (Gold, 1966).

The neurological complications, though uncommon, are among the most serious ones, with encephalitis and Guillain–Barré syndrome triggered by the infection being potentially life-threatening.

In this paper, neurological aspects of chickenpox in children, its long-term effects, and prevention methods are discussed.

EPIDEMIOLOGY

Varicella occurs with a worldwide geographical distribution. This α-herpesvirus, transmitted via an airborne route, shows a seasonal pattern with annual epidemics occurring most frequently during late winter and spring, typical for temperate climates. The highest, approximately 90%, risk of infection is linked to primary household contacts exposed to VZV without a history of vaccination (Ross, 1962). In the temperate climates, children usually acquire varicella during their first five to 10 years of life. Studies performed in Poland have demonstrated that the overall seroprevalence among the juvenile population rises steadily from 26% during the first year of life, up to 82% by the age of 10, to reach a maximum of 98% in the group of young adults in 19th year of life (Siennicka et al., 2009).

Worldwide, varicella affects nearly all children who do not have immunity to the disease. The annual incidence is estimated at 80–90 million cases. Due to the cost involved, developing countries have low immunisation rates, which results in a risk for travellers to such regions. In countries with routine varicella vaccinations, the incidence of varicella has been reduced by 76–87% (Vázquez et al., 2004).

PATHOGENESIS AND NEUROPATHOGENESIS OF VZV INFECTION

VZV invades the body through the upper respiratory tract and oropharynx mucosa and spreads rapidly to regional lymph nodes, where it undergoes the first phase of replication. After an interval of four to six days, primary, subclinical viraemia occurs, with the dissemination of the virus throughout the body via circulating T-lymphocytes.

The second viraemia leads to the appearance of an exanthem about a week later, following replication in reticuloendothelial system cells, and subsequent viral spread to the skin and the nasopharyngeal surfaces. The total incubation period is usually 14 to 15 days, with a range of 10 to 21 days (Whitley, 2020).

After the primary VZV infection, the virus becomes latent in the sensory root ganglia, which has been proven by polymerase chain reaction (PCR) and in situ hybridisation techniques (Mahalingam et al., 1990).

The neuropathogenesis of VZV infections is not well understood. It has been suggested that in the primary disease, the pathways of spread to the central nervous system (CNS) involve retrograde trafficking of the virus from the vesicles on the face to the trigeminal ganglion, and then via the ophthalmic branch to the cerebral arteries (Horien and Grose, 2012). Based on the presence of multifocal lesions at the grey-white matter junction in VZV CNS infections, the hypothesis of haematogenous spread of the virus has been proposed (Horten et al., 1981; Kleinschmidt-DeMasters et al., 1996). It has also been suggested that encephalitis associated with VZV reactivation is primarily a vasculopathy, and that symptoms of brain involvement may not be an effect of direct viral invasion but secondary to an inflammatory response within the large and small cerebral arteries, with the presence of VZV DNA and antigen, as well as multinucleated giant cells in affected vessels reported (Fukumoto et al., 1986; Gilden, 2002; Gilden et al., 2009, 1996; Miyazaki et al., 2008).

It seems that all the proposed mechanisms contribute to the clinical picture, with a direct cytotoxic effect of the virus and secondary neuronal ischemia, as well as infectious astrogliosis.

It is still debated whether cerebellitis has post-infectious, immune-mediated pathogenesis or a primarily infectious

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origin, as the detection of VZV DNA in the CSF of several patients has been reported. However, the phenomenon of pre-eruptive symptomatic cerebellitis preceding the rash indicates the viral infection of the CNS (Adams et al., 2000; Balfour et al., 2001; Barnes and Whitley, 1986; Fritzler et al., 2003; Uchibori et al., 2005).

NEUROLOGICAL MANIFESTATIONS OF VZV INFECTION

First, it should be mentioned that a vast majority of varicella and HZ cases in immunocompetent hosts are uncomplicated and self-limited. Among the complications of the VZV infection, the prime one is secondary bacterial infection, followed by transient hepatitis occurring in about 50% of children, varicella-associated pneumonia as well as impermanent thrombocytopaenia (Bollea-Garlatti et al., 2017; Raadsen et al., 2021).

VZV reactivation in the form of HZ may involve complications including cutaneous with bacterial superinfection and visceral with pneumonia, hepatitis, and ocular tissue inflammation. Infrequently, due to both primary and reactivated disease, neurological complications develop, particularly involving the CNS.

The incidence of CNS complications in children with chickenpox is 0.5–1.5 per 1,000, which is a lower number than in the pre-vaccine era (Barnes and Whitley, 1986; Gilden et al., 2002; Hall et al., 1983). The mean age of children in this group is four to seven years (Liese et al., 2008; Rack et al., 2010).

With respect to HZ, there are relatively limited clinical studies of children with that diagnosis due to its rarity in childhood, with a reported incidence of 0.74 per 1,000 in the group under nine years of age.

Although neurological complications in children are rare, as mentioned above, they become the second most common indication for hospitalisation of immunocompetent children with varicella (Pahud et al., 2011; Rivest et al., 2001; Science et al., 2014).

It is known that both immunocompetent and immunocompromised patients may suffer from neurological complications during VZV infection. Moreover, they appear to be more severe in the latter group (Gilden, 2002; Horien and Grose, 2012; Miyazaki et al., 2008). Regarding the frequency of these complications, ambiguous data exist, and studies report fewer neurological complications in immunocompromised children (Hall et al., 1983). An explanation for this phenomenon can be found in a recommendation for pre-emptive antiviral treatment in children with immunodeficiencies exposed to varicella, who are more effectively protected (Szenborn et al., 2016).

Varicella

Although the spectrum of nervous system diseases associated with chickenpox is broad, the division of those manifestations into several clinical syndromes is nevertheless possible. The main categories based on the predominant neurological abnormalities are: 1) acute cerebellar ataxia, 2) aseptic meningitis, 3) encephalitis, and 4) transverse myelitis. Other uncommon syndromes include Guillain–Barré syndrome, acute disseminated encephalomyelitis, and ischemic stroke.

Acute cerebellar ataxia (ACA)

ACA is the most typical neurological abnormality associated with childhood varicella, with the median age at 3–5.5 years (Bozzola et al., 2014, 2012; Cameron et al., 2007; Rack et al., 2010). Several series studies have reported the incidence of ACA as one per 4,000 children with VZV infection (Guess et al., 1986; Salas and Nava, 2010).

Typically the onset is acute, with the development of CNS abnormalities from several days before to two weeks after the beginning of the skin rash, and most commonly concomitantly (Dangond et al., 1993).

Characteristic symptoms consist of nausea, vomiting and headache, accompanied by ataxia with a broad-based gait, and dysarthria. In cases presenting before the development of the skin rash, the diagnosis may not be clinically apparent, and differential diagnoses may include cerebellar tumours, obstructive hydrocephalus, and other infectious and parainfectious causes.

The extent of the diagnostic evaluation in VZV-associated cerebellar dysfunction should be dictated by the uncertainty or severity of the illness. In uncomplicated cases, the clinical picture should be indicative of the diagnosis, with no need for further diagnostic evaluation. In more uncertain presentations, a lumbar puncture, electroencephalogram (EEG), or neuroimaging may be warranted. The general analysis of CSF reveals no abnormalities in the majority of cases. However, mild lymphocytic pleocytosis and elevated protein levels may occur in up to 30% of patients (Persson et al., 2009).

The EEG shows a diffuse slowing in the background activity in approximately 20% of cases, with normalisation evident as the symptoms resolve. The neuroimaging studies are expected to be normal in VZV-associated cerebellar ataxia. Complete recovery within several weeks is the norm, and even though persistent cerebellar deficits (such as hearing impairment) might occur, the overwhelming majority of children recover without sequelae (Bonhoeffer et al., 2005; Connolly et al., 1994; Marchetto et al., 2007). However, long-term follow-ups are lacking.

Encephalitis

The overall incidence of VZV-associated encephalitis in children is low, estimated at 0.2 per 100,000 children with an average of 5.4–6.4 years (Cameron et al., 2007; Rack et al., 2010; Ziebold et al., 2001).

In children, VZV has been recognised as the leading aetiological factor of encephalitis. In contrast, according to studies involving all age groups conducted in the Western world in recent years, this viral factor is the second most common

aetiology confirmed after the herpes simplex virus (HSV) (De Broucker et al., 2012; Granerod et al., 2010; Mailles and Stahl, 2009; de Ory et al., 2013; Vial et al., 2007).

Neurological symptoms may occur from 11 days before to several weeks after the onset of the skin rash (Appelbaum et al., 1953). The most frequently noted symptoms are altered mental status, and headache and vomiting, while seizures are less often reported, encountered in 29–52% of cases (Johnson and Milbourn, 1970). Focal neurological signs may include cranial nerve dysfunction, aphasia, and hemiparesis (De Broucker et al., 2012; Johnson and Milbourn, 1970; Mailles et al., 2012; Pollak et al., 2012).

In VZV-associated encephalitis, the general CSF analysis is frequently above normal reference values, with mild to moderate lymphocytic pleocytosis and elevated protein levels, and abnormalities more pronounced than in patients diagnosed with ACA (Science et al., 2014).

The EEG is often diffusely abnormal, with slowing background activity and epileptiform discharges which may occur even without clinically evident seizures. However, in symptomatic patients presenting with seizure activity, EEG abnormalities persist and are found in about 40% of follow-ups at one year (Gibbs et al., 1964; Hsieh et al., 2007; Ikeda et al., 2003).

In sparse studies analysing children among treated patients, the mortality rate is reported to be as high as 30–35% (Johnson and Milbourn, 1970; Science et al., 2014).

The case fatality rate remains high, and sequelae are frequent in all age groups. However, the exact data focusing on children are lacking (De Broucker et al., 2012).

Meningitis

VZV is reported to be the second most frequent causative pathogen of viral meningitis after enterovirus in patients of all ages, giving positive PCR results in 4.4% to 11% of cases (Hausfater et al., 2004; de Ory et al., 2013). Aseptic meningitis encountered with varicella is similar to that caused by other neurotrophic viruses. In children, this manifestation might appear with both primary and reactivated VZV. Meningismus and fever without evidence of cerebral dysfunction are considered suggestive for the diagnosis. General CSF analysis reveals mild lymphocytic pleocytosis combined with slightly elevated protein and normal glucose levels.

In children, the outcome in meningitis is overall favourable, with complete recovery and without any residual neurological disturbances, but follow-up studies are scarce (Bonhoeffer et al., 2005; Marchetto et al., 2007; Science et al., 2014; Ziebold et al., 2001).

Other

Transverse myelitis is an uncommon CNS manifestation that may occur as a complication of VZV infection, with symptoms appearing from days to weeks after the appearance of the skin rash. The clinical presentation is characterised by spinal cord involvement, bilateral paresis of the extremities, sphincter dysfunction, and sensory deficits combined with abnormal deep tendon reflexes and extensor plantar reflexes. The clinical picture reflects the distribution of nerve roots infected by VZV.

Complete recovery is an unusual outcome, with poorer results noted in immunocompromised patients (Hung et al., 2012). The exact data about VZV-associated myelitis in children are lacking, as mostly case reports concerning adult patients are available.

Vasculopathy caused by VZV in children is the most common cause of acute ischaemic stroke. The risk of developing stroke within the first six months after varicella is increased up to fourfold (Askalan et al., 2001). However, the overall risk of stroke associated with varicella is estimated to be one in 15,000 children with chickenpox (deVeber et al., 2000; Sébire et al., 1999). Apart from stroke and transient ischaemic attacks (TIA), where focal deficits depend on the location of infarction/artery occlusion, less obvious syndromes such as encephalitis have also been suggested to be VZV-associated vascular disorders (Gilden et al., 2009). As proven in several clinical studies, the prognosis in cases of VZV-associated stroke is poor, with just a minority of patients demonstrating complete resolution of symptoms at hospital discharge.

By definition, Reye's syndrome included encephalopathy and liver damage, and was associated with varicella and aspirin intake. The identification of this association has led to a reduction of aspirin intake in children. Hence Reye's syndrome is reported extremely rarely nowadays.

Herpes zoster

The neurological complications of shingles are the subjects of numerous reports. Distinct clinical syndromes have been described in the literature, including encephalitis, myelitis, leukoencephalopathy, cranial/peripheral nerve palsy and Guillain–Barré syndrome.

Cranial nerve palsies, including Ramsay Hunt syndrome

Zoster-associated palsy may affect most cranial nerves, but the trigeminal nerve is the one most commonly involved. The distribution of symptoms depends on the branch affected: the optic, the maxillary, and the mandibular nerve. Involvement of the ocular nerve may potentially lead to severe complications such as retinal necrosis. Another characteristic syndrome linked with VZV reactivation is Ramsay Hunt syndrome, characterised by peripheral facial palsy accompanied by a rash on the ear, often referred to as zoster oticus, and potentially associated with CSF pleocytosis, indicating CNS involvement (Persson et al., 2009). Involvement of the vestibulocochlear combined with the facial nerves can cause vertigo, deafness, tinnitus, and nystagmus.

In children, no studies of cranial nerve palsies, including Ramsay Hunt syndrome, have been performed. However, the complication occurs considerably less

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frequently (Koskiniemi et al., 2002; Rack et al., 2010; Science et al., 2014; Ziebold et al., 2001), and few long-term sequelae are reported. In adults, the risk of permanent facial palsy in patients with Ramsay Hunt syndrome depends not only on the severity of the palsy, but mainly on the prompt initiation of treatment, preferably with acyclovir and steroids which have been proven to result in the highest recovery rates (Kinishi et al., 2001; Uri et al., 2003).

Guillain–Barré syndrome

Polyneuropathy in the form of Guillain–Barré syndrome is reported more frequently after reactivated VZV (Islam et al., 2018; Laurenti et al., 2002). Characteristic symptoms – with gradually developing weakness leading to quadriplegia, sensory symptoms and cranial nerve dysfunction – seem to develop longer in zoster-associated disease (Islam et al., 2018). The diagnosis usually poses no challenge, as CSF albuminocytologic dissociation is noted in the vast majority of patients.

DIAGNOSIS OF VZV INFECTION

As the vesicular rash typical for VZV infection is so characteristic, establishing a clinical diagnosis usually poses no difficulty. In disputed cases of varicella, epidemiological information focused on a history of possible recent exposure to varicella or zoster, may be useful. The differential diagnosis of varicella includes generalised HSV infection, enterovirus infections, impetigo, allergic reactions (including Stevens–Johnson syndrome), and insect bites.

For an indisputable diagnosis of CNS infection caused by VZV, the detection of VZV DNA in CSF with the PCR method is necessary. It should be stressed that a negative result of the PCR test does not rule out VZV infection, especially after the initiation of antiviral treatment, hence testing should be conducted prior to the first doses of antivirals. Another way of confirming CNS infection with VZV is by measuring anti-VZV antibodies. A significant increase of anti-VZV antibody titre in CSF throughout the illness or findings suggesting the intrathecal production of antibodies, represents an unequivocal confirmation of CNS involvement.

THERAPY

As neurological complications of VZV infection seems to be caused predominantly by VZV replication in the CNS, the apparent goal of the treatment is the inhibition of replication.

According to the recommendations, antiviral therapy with intravenous acyclovir should be implemented as soon as the diagnosis is considered. There have been no controlled studies to validate that recommendation, probably due to underestimating the number of patients with VZV CNS disease. Although the prognosis of meningitis is good, encephalitis and myelitis may result in sequelae. Consequently, a delay in the initiation of the antiviral treatment leads to a poorer result, so the clinical suspicion of VZV-associated CNS infection should prompt the initiation of therapy.

In Poland, the current recommendations in children with CNS manifestations include intravenously given acyclovir 10–20 mg/kg, 3 times daily for seven to 21 days, depending on the immunological status and specific diagnosis. These guidelines are in line with the recommendations of other medical societies (Britton et al., 2015; Gilden et al., 2005; Gnann, 2007; Pahud et al., 2011; Stahl et al., 2017; Tunkel et al., 2008).

In vasculitis and cranial nerve palsies, additional steroid therapy may be considered to reduce the inflammation in the CNS (Szenborn et al., 2016).

CONCLUSION

Due to its high contagiousness, VZV affects nearly all susceptible children, mainly before the age of adolescence. Despite generally being considered a mild and self-limiting illness, even today the disease may not be benign, with a significant number of varicella cases being associated with complications. The majority of children with neurological complications of varicella present a complete recovery without any residual neurological disturbances; however, most VZV-inducted CNS complications present as cerebellitis, and only few long-term follow-ups exist. As no correlation between the severity of varicella and its complications has been found, clinicians should be aware of neurological symptoms induced by VZV, as early antiviral treatment is necessary for a favourable outcome. It should also be stressed that in the era when a safe and effective vaccine against chickenpox is available, its popularisation could help reduce the number of patients suffering from neurological complications of the disease. It is advisable to encourage vaccination, and to take active steps to introduce this vaccination into the population immunisation schedule.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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