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Advances in the diagnostics of Varizella zoster virus and importance of vaccination[1)]

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Abstract

Varizella zoster virus (VZV) belongs to one of the eight herpes viruses known to infect humans.

While primary VZV infection (chickenpox) is generally a disease of childhood, herpes zoster occurs primarily in elderly persons (>50 years). Herpes zoster, also called shingles, is a neurocutaneous disease resulting from reactivation of latent varizella zoster virus infection within dorsal root ganglia.

Severe complications may occur in elderly and in immuno-compromised persons, including severe complication of the eye, the ear, the skin, internal organs, and the peripheral and central nervous system. A progressive decline of VZV-specific cell-mediated immunity and age are associated with an increased incidence and severity of herpes zoster and postherpetic neuralgia (PHN).

PHN is the most common complication of herpes zoster causing chronic, debilitating pain. In cases with characteristic signs and symptoms (presence of prodromal pain, eruptions, grouped vesicles, segmental pain) the diagnosis is almost distinctive enough and no laboratory investigations are required. However, for patients lacking no characteristic pathology, a rapid laboratory diagnosis may be helpful to start antiviral therapy as soon as possible. Antiviral therapy should be initiated immediately within 72 h after onset of rash particularly in older patients. The major aim of treatment is to control and reduce the acute zoster pain, to shorten virus replication, to avoid dissemination of skin lesions and to prevent PHN and other severe complications The aim of the present review is to outline advantages and disadvantages of different laboratory methods of herpes zoster (microscopy, direct immunofluorescence assay, detection of viral DNA, virus isolation and serological methods. A live attenuated VZV vaccine has been developed to prevent herpes zoster and postherpetic neuralgia in individuals beyond 60 years of age (Shingles Prevention Study). This review summarises the epidemiology, pathogenesis, clinical aspects, complications, therapy and prevention of varizella zoster.

Keywords: herpes zoster; laboratory testing; prevention; treatment; vaccine.

Herpes zoster (shingles) is a neurocutaneous disease, defined as the endogenous reactivation of latent varizella zoster viruses (VZV) persisting within ganglion cells following primary infection (Windpocken). While primary VZV infection (chickenpox) is generally a disease of childhood and adolescence, an endogenous reactivation (herpes zoster) occurs primarily in elderly persons (beyond 50 years of age). The course of recurrent infections varies largely. Prompt antiviral therapy is however indicated, if a severe disease course (e.g., infection of the head) is anticipated. Postherpetic neuralgia (PHN) is one of the most feared complications. It is a painful, persistent, sometimes life-long condition, the incidence of which increases with age.

A decline in the incidence of chickenpox has been observed since a general VZV vaccine was marketed (2004). However, the number of zoster cases, which impacts the health care system significantly more than chickenpox, increased at the same time, since subclinical abortive infections cease to exist as wild virus immunity boosters.

In order to counteract these adverse effects, a 14-fold concentrated herpes zoster vaccine was developed in the US, which reduced the incidence of VZV and the risk of PHN in a field study [1]. This high dose VZV vaccine is indicated for use in patients beyond 60 years of age, and even better earlier, in order to reduce the incidence and potential risks of herpes zoster.

Etiology

Varizella zoster virus (VZV) is one of the eight herpes viruses known to infect humans. It belongs taxonomically to the group of alpha herpes viruses.

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Its double-stranded, linear DNA, consisting of about 125-kilobase pairs, is encased within an icosahedral protein capsid, composed of 162 capsomers. The nucleocapsid is surrounded by a pleomorphous outer shell (tegument with envelope membrane), which is rich in phosphoprotein. Diameters vary between 150 and 180 nm due to the variability of the outer shell [2].

Epidemiology

With its ubiquitous presence, varicella is widespread among the population. It is mainly spread among children. More than 90% of young adults are showing immunity towards exogenous infections [3, 4]. Every latently infected person is at risk of developing herpes zoster (shingles). Carriers of antibodies are also virus carriers.

The chickenpox virus is transmitted via aerosols (airborne). Initially, multiplication of the virus takes place at the portal of entry (Waldeyer's tonsillar ring). A primary, often subclinical viremic phase follows, characterized by infection of different visceral organs (latent virus replication). The skin, which is the main target organ, is affected during a secondary viremic phase. Varicella is characterized by a distinguished rash. The concurrent existence of these typical skin eruptions (macules, papules, vesicles, and pustules) is known as a "star chart". Prognosis is generally good for varicella, but in rare cases, VZV induced pneumonia or encephalitis have been observed. When sensory nerve endings are infected, life-long, persistent infections are established. The virus reaches the spinal ganglion through the cytoplasm of the neuron. The virus genome (DNA) is ejected from the capsid and enters the nucleus of the spinal ganglion cell, where it persists in the form of a latent and largely inactive ring (episome). The molecular signals maintaining the mechanism of this suppression are not known. It is assumed that an interaction between cytokines released from T-lymphocytes and specific DNA transcripts takes place [2]. It was shown using in situ hybridization, that DNA transcription is not completely shut off during the latent phase, but restricted to a few specific genes (ORF 4, 21, 29, 62, 63, 66). Genes ORF 62 and ORF 63 are associated with histone acetylation [5].

If after many years following the primary infection the number of memory cells for T-lymphocytes is markedly reduced or depleted, the neuron-specific suppression may be removed. As a result, the synthesis of new virus particles begins (massive virus reactivation), causing the formation of varicella-like skin eruptions (shingles) along the respective sensory nerves in the area of the associated dermatome. It is assumed that the preferred dermatome of the body is the one which had the highest viral load within its ganglion or sensory nerve during primary infection. The immunostimulation induced by herpes zoster usually protects other dermatomes of the body, with the exception of an immature or iatrogenically compromised immunosystem.

Clinical appearance of herpes zoster

About 80% of patients reported prodromal pain, paresthesia, and occasional pruritus in the affected dermatome prior to the formation of the first characteristic skin eruptions [6]. Further accompanying symptoms are fever, headache, and lymph node swelling.

Prodromal symptoms are either localized in a dermatome or occur independent of a dermatome. The duration of this phase is usually one to five days. In rare cases, it can last up to three weeks [6]. Characteristic skin eruptions appear subsequently. First, a unilateral erythema develops in the affected dermatome, followed by a maculopapular rash. The resulting blisters can later become confluent and dry up in several stages. New blisters are formed over a period of one to seven days [6]. Dermatomes in chest and head areas are most severely affected. Herpes zoster eruptions in lumbar, sacral, and cervical segments are observed in rare cases. Bilateral eruptions also appear in $<1\%$ of all cases [7]. In patients with a healthy immune system, the healing process is expected to be completed after two to three weeks following herpes zoster breakout, while in immunocompromised patients, a chronic herpes zoster infection with recurring skin eruptions can develop. In rare cases, a prodromal phase is followed by isolated dermatome-dependent pain without the development of characteristic skin eruptions. This condition is known as "Zoster sine herpete" [8].

Complications and consequences of herpes zoster

Cutaneous complications Acute and chronic complications affecting skin, eyes, ears, and the central nervous system are quite common, while only few complications affecting internal organs (pneumonia, esophagitis, enterocolitis, pancreatitis, and arthritis) have been described. Cutaneous complications include bacterial superinfections, ulcerations, hemorrhage (zoster haemorrhagicus), ulcerous colliquations (Zoster gangraenosum), and Zoster disseminatus, which is characterized by persistent lesions and dissemination and occurs predominantly in immunocompromised patients. Long-term complications include hypo- and hyper-pigmented scar formation, rare granulomatous reactions, and psoriasis vulgaris [9].

Neurological complications These complications include herpes zoster-associated meningitis, segmental paralysis, neuropathies, granulomatous arteritis, as well as fascialisparesis associated with herpes zoster oticus. Chronic complications of the CNS include Guillain-Barré Syndrome, paralyses (paralysed diaphragm), abdominal hernias, bladder insufficiencies, and herpes zoster associated pain [9].

Herpes zoster ophthalmicus Herpes zoster ophthalmicus is characterized by localized pain and skin alterations along the first division of the trigeminus. The eye

lids as well as other parts of the eye can be affected (redness and swelling with possible formation of eyelid scars). The majority of patient present with ptosis. Since the N. trigeminus also innervates the cornea, corneal ulcer is observed in 20–70% of the cases. Without antiviral therapy, ophthalmological complications might develop in more than 50% of patients [10]. Chronic complications include ceratitis, choreoretinitis, neuritis, retrobulbar neuritis, vasculitis, panophthalmitis, and atrophy of the N. opticus [9, 11].

Herpes zoster oticus Herpes zoster oticus is seen most commonly in the elderly population or in immunocompromised patients, but might also be associated with stress in younger people [12]. Particularly when children are diagnosed with acute facial paresis, reactivation of herpes zoster needs to be considered [13]. Clinical presentation and severity vary from one case to the next. Typical symptoms include periauricular pain, hepetiform skin alterations, and nerval dysfunctions, mostly of the VIIth and VIIIth, sometimes the Vth, IXth, and Xth cerebral nerves [14].

Herpes zoster-associated pain

This includes acute herpes zoster pain as well as postzoster neuralgia (synonym: postherpetic neuralgia), which is the most common complication of herpes zoster [15]. Various definitions can be found in the literature. Dworkin (1997) defined PHN as typically pain, which may persist for three to six months following the acute infection [16]. This pain is neuropathic pain, which is characterized by a burning sensation.

The risk of PHN increases with increasing age. Postherpetic neuralgia is rarely seen in children [17], while older patients with herpes zoster show manifestation rates of 27% (patients beyond 55 years of age), 47% (patients beyond 60 years of age), and 73% (over 70-year-old patients) [9]. Prognostic factors associated with PHN include increasing age as well as prodromal syndromes, strong initial dermal pain, female gender, and zoster ophthalmicus [9, 18, 19]. The associated persistent pain, which is often difficult to alleviate therapeutically, may cause physical and psychological restrictions, including weight loss, fatigue, and depression [20]. These patients are suffering a significant loss of their quality of life. Years of pain management and alternative therapy procedures are an increasing burden on patients and health care systems.

Diagnosis

The diagnosis of herpes zoster is based on the characteristic clinical presentation and the patients' medical history. In less unambiguous cases, e.g., immunocompromised or pregnant patients, neonates, and patients with suspected central nervous system (CNS) infections, a diagnosis based on clinical findings must be confirmed quickly in order to initiate targeted therapy in a timely fashion.

In the presence of vascular skin eruptions, utilization of direct virological detection methods, i.e., blister puncture and/or blister swab is recommended.

A virus can be classified into its respective herpes group electronmicroscopically, but this method does not allow any further differentiation of the herpes virus. Electronmicroscopy is therefore not used as a routine diagnostic tool.

Virus isolation from cell cultures is very sensitive when sample collection is optimal. For positive tests, it remains the most reliable virus detection method [21]. It is, however, sometimes less sensitive than the analysis of sample swabs using immunofluorescence technique (IFT), since the viable virus in the blisters is considerably less stable than viral antigen [22]. The length of time for conventional virus isolation does not allow any manipulation of the clinical decision in urgent cases, since the virus concerned is instable, strongly cell associated, and replicates very slowly in cell cultures, especially when virus titers are low [22]. The method can, however, provide a confirmation of the diagnosis and be used for resistance testing in therapy resistant cases. It should be noted that the isolation of VZV from strains with acyclovir resistance is particularly difficult. As a general rule, human fibroblasts from embryonic skin, lung tissue, or human foreskin cells are used. Furthermore, human retinal pigment epithelial cells (RPE) can be used. They serve as a cell culture model for determination of viral neurotropism. Even under optimal conditions, a significant number of inoculated cell cultures remains CPE negative (CPE = cytopathical effect), even though VZV antigen tests and DNA tests are positive [23–25]. The technique of modified rapid virus isolation ("shell vial assay") therefore increases sensitivity and allows the detection of additional viral antigen and DNA in the infected cell culture and thereby a more rapid virus detection (length of time: one to three days).

Polymerase chain reaction (PCR) has become the method of choice when CNS infection is suspected, eyes are affected, and VZV-associated vasculopathies are confirmed [26–28]. It is the most sensitive and most specific method of VZV detection in liquor and eye chamber water, which can detect VZV genome in blister fluid, even after antiviral therapy was initiated [25]. The detection of viral genome does not indicate the presence of an infectious virus. Consequently, results of this highly sensitive method will always have to be interpreted along with clinical findings [29]. The quantitative PCR method most commonly used today is the "real-time" technique. It allows quantitative detection of small amounts of virus genome in latently infected ganglion cells. In certain cases, molecular characterization of VZV isolates can be achieved using DNA sequencing [30]. This approach is useful in the detection of mutations associated with acyclovir resistance or for determining relationships among

clinical isolates for epidemiological purposes. The introduction of real-time PCR resulted in a faster procedure, improved sensitivity and an extended linear measuring range when determining the viral load.

A fast and specific diagnosis of lesions suspicious of VZV can be obtained using direct immunofluorescence testing for the detection of virus antigen. The assurance of optimal sensitivity requires cells to be scraped off the bottom of freshly punctured blisters. The sensitivity of this procedure is a function of the sample collection quality. In patients with "Zoster sine herpete", antigen detection is problematic, and the use of all known methods of VZV detection is required.

Chickenpox and herpes zoster are often diagnosed using serological tests. Preferred procedures are the highly sensitive and specific enzyme-linked immunosorbent assays (ELISA). Using ELISA and immunofluorescence technique (IFT), VZV-specific immunoglobulines of all three major classes (IgG, IgM, and IgA) can be detected. In acute primary infections, IgM antibodies can be detected in addition to IgG antibodies (which often appear first with VZV). After reactivation, detection of IgM, is, however, less sensitive. VZV-reactivations often induce a significant IgG and IgA antibody increase [31], which is seen in about 50–60% of patients [24, 32]. With both primary infection and reactivation, cross reactions between HSV and VZV antibodies occur. Differentiation requires additional testing, studies of the clinical course and/or supplementary clinical information. In patients with pain syndromes or facial pareses resulting from "zoster sine herpete", increased VZV-IgG values may provide additional information to clarify the etiology [33]. Since the VZV virus is highly instable, the neutralization test should be neglected as a routine serological procedure in VZV diagnostics.

Dobec at al. (2008) conducted a study with 53 herpes zoster patients and showed that optimal sensitivity in the early diagnosis of VZV reactivation is obtained with a combination of PCR (real-time) and serology using paired serum samples [34].

Differential diagnoses

Zosteriform herpes simplex and various manifestations of erysipelas play an important role in the differential diagnosis of herpes zoster of the skin. Furthermore, contact dermatitis (pruritus), insect bites, and bullous dermatoses (bullous pemphigoid, pemphigus vulgaris) represent a challenge in differential diagnosis. Rare differential diagnoses are phlegmons and panniculitis.

Prior to the eruption of skin lesions, patients report various pain syndromes and paresthesias which can result in misdiagnoses, including glaucoma, disc prolapse, acute coronary syndrome, cholecystitis, duodenal ulcer, renal or hepatic colic, appendicitis, or lumboischialgia.

Therapy

Treatment of acute herpes zoster pain

Early initiation of antiviral therapy (within the first 72 h) should be accompanied by pain management. Sufficiently high dosages and a sufficient duration of therapy are important for the prevention of pain chronification. Each long-term pain stimulus of the central nervous system can promote chronification. Pain medications used include non-steroidal antiphlogistics (e.g., acetaminophen), weak opioids (e.g., tramadol, codeine), and highly potent opioids (e.g., buprenorphine, morphine) for very strong pain. In one study, administration of 50 mg amitryptilin during the acute phase could reduce the PHN incidence by half [35]. Additional therapy with high doses of glucocorticoids affected the duration of acute herpes zoster pain favorably, but did not effect the incidence of PHN markedly [36, 37]. A combination of virustatic medications, analgetics, and certain co-analgetics (anitdepressants, anticonvulsives) seems to minimize the chronification risk and consequently the development of PZN [38].

Treatment of postzosteric neuralgia

Results from various randomized clinical control studies demonstrated the effectiveness of antidepressants, opioids, anticonvulsives, and topical analgesics [39]. Since several mechanisms contribute to the development of PHN, the early start of a combination therapy with low doses of medications from two or more pharmaceutical groups is indicated. Combination therapies are more successful and show less side effects than monotherapies with higher doses of medication [40].

Indications for systemic therapy

Systemic therapy is indicated in all patients 50 years and older, in all cases where herpes zoster affects head or neck areas (Z. oticus, Z. ophthalmicus, affection of cerebral nerves), in immunocompromised patients, patients with widespread zoster affecting trunk and extremities, and patients with severe dermatitis atopica and other widespread eczemas. Herpes zoster on the trunk and extremities of younger patients ($<$50 years) is a relative indication for systemic therapy [41].

In Germany, four antiviral agents are approved for antiviral herpes zoster therapy (Table 1). For Aciclovir, an oral and intravenous dosage form exists. Aciclovir is not effective when applied locally. Aciclovir was shown to be effective in various studies, and was therefore chosen as standard treatment of herpes zoster for many years [42]. Compared to Aciclovir, Valaciclovir and Famciclovir both show increased bioavailability and improved pharmacokinetics following oral administration. Consequently, they have replaced Aciclovir in the oral treatment of uncomplicated herpes zoster. Further placebo-controlled studies also demonstrated that Valaciclovir was superior to

Table 1 Antiviral therapy of herpes zoster.

Virustatic agent	Doses		Duration of therapy
Aciclovir i.v.	Immunocompetent patients: 5–7.5 mg/kg KG	3×daily	7 days
	Immunodeficient patients: 8–10 mg/kg KG	3×daily	7–10 days
Aciclovir orally	800 mg	5×daily	7 days
Valaciclovir orally	1000 mg	3×daily	7 days
Famciclovir orally	250 mg	3×daily	7 days
Brivudin orally	125 mg	1×daily	7 days

Aciclovir in terms of alleviating zoster-associated pain and ocular complications [43, 44]. The antiviral potency of Brivudin, which persists much longer in the infected cells due to its long plasma half-life, is significantly higher than that of the nucleoside analogs listed and used for therapy so far. It is superior to the other listed medications listed, due to its simpler dosing pattern (once daily) and proven effectiveness. Wutzler et al. showed that Brivudin stopped virus replication faster than oral Aciclovir [45]. Another randomized study also demonstrated superiority of Brivudin vs. Aciclovir in terms of postherpetic neuralgia. Only 32.7% developed postherpetic neuralgias, 11% less than in the Aciclovir group, where 43.5% developed PHN ($p < 0.006$) [46]. Brivudin and Famciclovir were equivalent in terms of their effect on duration and pain associated with herpes zoster [46]. Restrictions apply to Brivudin therapy when treating immunocompromised, pregnant, and nursing patients as well as children.

Brivudin is also contraindicated in patients receiving 5-fluoro-uracil (5-FU). An irreversible inhibition of the enzyme dihydropyrimidine dehydrogenase prevents 5-Fluorouracil from being metabolized, and increases toxicity [47]. If resistances to the nucleoside analogs listed develop, particularly as a result of long-term therapy of chronic VZV infections, Foscarnet remains the reserve drug of choice.

Vaccine

A large randomized and double-blind American study (Shingles Prevention Study) tested 38,567 sixty-year-old subjects vs. placebo [1]. The study was based on the hypothesis that a zoster vaccine would lower the incidence and/or severity of herpes zoster infections and PHN. A live vaccine was developed, which had at least 14-fold higher concentrations than the varicella vaccine on the market. This zoster vaccine was injected subcutaneously once. Inclusion criteria were positive varicella history and negative history of herpes zoster. Zoster infections were determined based on clinical and laboratory data. During the median follow-up period of little more than three years, 957 zoster cases were confirmed (315 in the vaccine group, 642 in the placebo group), showing a significant decline of zoster incidence in the vaccine group (51.3%). Furthermore, the clinical course was milder with less complications in the vaccinated group. The vaccine group also had a 65% reduced risk of postherpetic neuralgia (development of postherpetic neuralgia: 27 in the vaccine group, 80 in the placebo group) The “burden of illness”, which describes incidence, duration and severity of zoster-associated pain as well as other conditions, could be reduced by 61.1% in the vaccine group. Side effects were observed more frequently in the vaccine group, but they were of mild character. Study data allow the conclusion that patients will be protected for at least 48 months. In May of 2006, the zoster vaccine tested was approved by EMEA (European Medicines Agency), but solely for the frozen variant. The target group were patients more than 60 years old. Since people under the age of 60 also have high incidences of zoster infections, the minimum age should be lowered to 50 years or even less.

Several studies demonstrated that risk and severity of zoster infections correlate to the progressive decline of cell mediated immunity [47]. Since use of the varicella vaccine leads to reduced wild virus boostering, it is recommended that zoster vaccine is applied individually when indicated. Except for their virulence, wild virus and vaccine virus continue to show strong similarities. Critics of vaccines are, however, appeased by the fact that we are still dealing with an immunity producing measure copied from nature. Potential vaccine virus alterations are monitored using genotyping (e.g., back mutations). Due to steadily increasing life expectancies among the population, herpes zoster is expected to become more and more of a problem. The “Shingles Prevention Study” clarifies the advantages of preventive use of zoster vaccines.

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