Herpes Zoster: New Preventive Perspectives

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INTRODUCTION

Herpes Zoster (HZ) is a well-known disease from ancient times [1] caused by varicella zoster virus (VZV), a Herpesvirus, airborne transmitted or/and by direct contact with skin lesions of a patient. The reservoir of infection is exclusively human and the virus typically spreads with an endemic-epidemic trend affecting mainly pediatric age [2]. The primary infection results in varicella (chickenpox) that is highly contagious and results in the development of VZV specific humoral and cell-mediated immunity (CMI) [3]. During primary infection, VZV is transported in a centripetal direction to the corresponding ganglionic neurons, where it remains quiescent establishing a lifetime immune-controlled infection (latent infection). The onset of HZ is a multi factorial process; events occurrence is closely related to a CMI decrease. The decline of CMI is strictly age-dependent, greatly increasing with age [4]. VZV, reactivated within sensory ganglia, causes neuronal necrosis, intense inflammation and neuritis; then the virus reaches the skin or mucosal surfaces innervated by the affected neuronal segment, where it replicates, producing the characteristic cluster of vesicles. In many patients, the rash with typical dermatomeric distribution and radicular pain completely disappears in 1-2 months [5]. The HZ associated pain reveals VZV neurotropism and can assume a chronic course, named postherpetic neuralgia (PHN) that can persist for at least 1-3 months after the eruption [6]. The estimated risk of developing HZ during lifetime is 10-30%, with a marked rise with increasing age, up to 50% in individuals over 85 years. A role in HZ onset can also be played by gender, seasonality, race, psychological stress, mechanical trauma, immune toxic chemicals and genetic predisposition [7].

HZ incidence is worldwide comparable, without seasonal and epidemic trend, and related to aging. Approximately two-thirds of cases occur in people older than 50 years [8] and one person out of four will develop HZ during life [9]. The international literature describes 2-3 cases per 1000 person-years between 20 and 50 years of age, 5 cases per 1000 person-years in the sixth decade and 6-7 cases per 1000 person-years in the seventh to eighth decade of life. Over 50 years old subjects experiencing HZ may suffer a significant decrease in quality of life [10]. The incidence increases markedly with age, becoming four times higher among older individuals aged over 70 years compared to those younger than 60 years [11]. Therefore due the aging population, an increasing incidence of HZ cases can be expected in the future [12]. HZ usually occurs only once in life; anyway, recurrence rate may be about 4-5% [13]. Complications occur in 13-40% of cases [14]; the most frequent is PHN [15] whose incidence, affected by different definitions and by the age of the patients observed, is generally estimated between 10 and 20% of cases of HZ (up to 30% in the elderly) [16]. Generally 80% of all PHN cases occur in individuals over 50 years of age [17].

CLINICAL FEATURES AND THERAPY

HZ is characterized by a vesicular rash and pain with dermatomal distribution [18]. The reactivation of latent VZV includes a prodromal phase, which occurs 1-5 days before the onset of the rash in 70%-80% of cases [19], characterized by an immune response and a neuronal cell inflammation. Prodromal symptoms are usually non-specific [20]. In the acute phase of the
disease, VZV infects cells of the dermis and epidermis, generating a rash, which usually affects a single dermatome. The unilateral dermatomal rash can be clinically divided into four stages: erythematosus, vesicular, pustular and ulcerative [21].

The HZ generally involves dermatomes from T1 to L2, and the first branch of the trigeminal nerve, but it is not uncommon that patients can develop lesions in adjacent dermatomes [22]. With increasing age more cranial lesions, including opthalmic, and less involvement of the chest are observed. During non-vesicular phases, the patient is not contagious. Along with eruption, most patients have a dermatomal pain syndrome caused by acute neuritis, described as a burning and deep pain, pricking, lancinating itching or pain, mild to severe [23]. The HZ acute pain is probably the result of a combination of nociceptive pain caused by inflammation of the skin and neuropathic pain caused by neuronal injury [24]. The chronic phase is represented by PHN that arises when the pain continues even after the rash has healed. In addition to old age, the increased severity of acute pain and the gravity of the rash are risk factors for PHN [25]. PHN is the most debilitating aspect of HZ and its most common complication. The patient with PHN may experience pain as a constant (described as burning or pulsating pain), intermittent (as lancinating or feeling of tension), or arising from stimuli that are not normally painful (allodynia). Moreover, PHN can compromise the functional status of elderly patients by interfering with basic activities of daily living.PHN is usually defined as a long-term chronic HZ-related pain that occurs or persists at least 3 months after the onset of rash or acute pain caused by shingles, also taking into account the intensity of the pain that is expected to reach a value of at least 3 in a visual analogical scale (VAS) from 0 (no pain) to 10 (maximum imaginable pain). Some recent perspective studies have assessed the persistence of symptoms until 10 years after the onset of HZ, recording painful episodes with functional nervous alterations. Other major complications, although less frequent, in elderly or immune compromised subjects, are: disseminated zoster, ocular inflammation with visual disabilities [26-27], stroke [28], focal motor paralysis. Another complication is the Ramsay-Hunt syndrome that occurs when VZV affects the geniculate ganglion of the facial nerve presenting itself as a unilateral facial paralysis accompanied by a vesicular rash in the external ear canal, in the ear flap or tympanic membrane, or involving hard palate or tongues [29]. The first goal of treatment aims to accelerate the recovery of the eruption, to relieve the pain and to reduce complications [30]. Although several progresses in HZ and PHN treatment has been made, available therapeutic options, using anti-viral, anti-inflammatory and analgesic drugs, are only partially effective. Antiviral therapy is more effective if started within 72 hours after the appearance of the rash [31], but the early diagnosis of HZ is often difficult because of the delay in seeking doctor’s advice.

Guidelines recommend oral antiviral agents for 7 days in patients with HZ who are at risk of developing PHN (patients over 50 years old with serious acute pain, severe rash, or significant prodromal symptoms) [31]. Despite the combined use of tricyclic antidepressants, anticonvulsants (gabapentin and pregabalin) and analgesics, PHN is often refractory to pharmacological treatments and to prevention strategies [32,33].

VACCINATION

Considering the epidemiological impact, the complications, and the costs of drug treatment (that is often suboptimal), a preventive approach was urgently needed. Some investigators have suggested a specific intervention to decrease the frequency and the severity of HZ; during the years, it has been confirmed that the vaccines for chickenpox, mainly those with high antigenic content, elicit a significant increase in cell-mediated immunity. Currently a vaccine against HZ has been licensed. It is a live, attenuated cell-free preparation of the 0ka strain of VZV used for paediatric variella immunization, but with a greater average power, equal to 24,600 PFU (antigen content at least 14 times higher than the chickenpox vaccine used in childhood) [34]. In 2006, the United States Food and Drug Administration (FDA) first approved the vaccine for over 60 years of age subjects and in 201, also for adults aged between 50 and 59 years on the basis of an extensive safety and efficacy study in this age group (ZEST) [35-36]. In Europe the authorization was granted in May 2006. The vaccine, available as a powder and a solvent to be reconstituted in suspension for injection, is indicated for the immunization of individuals 50 years of age or older and is administered subcutaneously as a single dose of 0.5 ml in the deltoid region of the arm [37].

The clinical efficacy of the vaccine has been demonstrated in two large phase III studies in over 60 years old subjects (SPS) and in 50-59 years old individuals (ZEST). HZ vaccine significantly reduces the risk of developing the disease and PHN and it also has an effect on the burden of illness associated with HZ. The study SPS [33] showed that the use of the vaccine led to a significant reduction in the incidence of shingles of 51.3% (95% CI= 44.2-57.6) and decreased PHN incidence by 66.5% (95% CI=47.5-79.2). In the group aged between 60 and 69 years, the incidence was decreased by 63.9%, compared to 37.6% of the population 70 years old and 18% in those over 80 years, proving to be less effective in older people. During the SPS study, it was also demonstrated that the HZ vaccine was safe and well tolerated [33].

The ZEST study included 22,439 subjects aged 50-59 years, showing an efficacy of 69.8% (95% CI= 54.1-80.6) in the prevention of HZ during follow-up (mean 1.3 years) [38]. A study of persistence in the short term (STPS), started in 2004 as a secondary study of the SPS with the aim to continue to monitor the effectiveness of the HZ vaccine, was conducted on a subset of 14,270 subjects from 4 to 7 years after vaccination and showed an efficacy of 39.6% (95% CI= 18.2-55.5) for the prevention of HZ and 60.1% (95% CI= 9.8-86.7) for the prevention of PHN [39].

The LTPS, extending the follow-up to 12 years after vaccination, assessed the duration of protection against HZ and PHN in about a third of the subjects previously vaccinated in SPS and STPS studies (6,867 subjects). The estimated vaccine efficacy (in over 70 years old subjects) was 21% for the incidence of HZ and 35% for the incidence of PHN.

The profile of effectiveness has been confirmed by other studies indicating an adequate level of protection against HZ and PHN [40,41].
DISCUSSION AND CONCLUSION

HZ is a very common disease that can be associated with severe complications with a negative impact on quality of life. Despite the widespread of the disease, rapid and early diagnosis and treatment are sometimes missed. The most common complication is PHN, a severe chronic pain that can persist for months or even years. Since effective treatment, with tolerable side effects, is a major clinical challenge and the proportion of frail and elderly population is increasing, preventive strategies are essential.

In conclusion, the currently available vaccine has a good profile in terms of immunogenicity and efficacy, also supported by effectiveness studies, while the data of follow-up (STPS and LTPS) showed persistent efficacy, even if the protection progressively decreases over time and with increasing age of the patient. It seems evident therefore the favorable profile of HZ vaccine, whose use could have a positive impact on the health of vulnerable elderly, helping to provide to the target population an healthy aging, free from pain and complications by HZ, first of all PHN.

CONFLICT OF INTEREST

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