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Herpes zoster in older adults and worsening of life quality

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Case Report

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Abstract

We present 3 cases of older adults who were diagnosed with herpes zoster, and had post herpetic neuralgia afterwards. One of them presented difficulties in the management of pain due to intolerances to different painkillers; our second patient had ophthalmic herpes zoster, and despite correct medication and strict adherence to indications, continued with pain almost two years later with severe interference in her daily life. The third one presented a diagnostic challenge because as time went by and pain evolved, she begun to lose weight, and deteriorated her general condition. She was finally diagnosed with terminal colon cancer for which she died a few months later.

All three cases show the difficulty of treatment and the interference of pain in daily quality of life. We reviewed the literature and updated the topic of post herpetic neuralgia, its diagnosis, management, prognosis and prevention.

Keywords: Herpes Zoster; Gabapentin; Pregabaline

Case Report Number One

Eighty one year old woman, with a medical history of gastritis, glaucoma, osteoporosis and dyslipidemia. Chronically medicated with omeprazole, statins, Timolol eye drops, and risedronate. On July 2014, she consulted the Emergency Department for an acute chest pain and blisters which begun less than one day earlier. She was diagnosted Herpes Zoster (HZ) and prescribed with oral aciclovir 800 mg every 4 hours, 5 times daily, for 5 days. As the patient was in pain, she was advised to take nonsteroidal pain killers with vitamin B.

Two days later, she got up in the morning feeling generalized malaise, dizziness, and generalized weakness. She finally fainted, and had to be carried again to the emergency room (ER) for an encephalocranial trauma with loss of consciousness and cutaneous injury in the occipital region. As she was examined she HZ blisters could be seen in dorsal and sub mammary region, a cutting wound without active bleeding in occipital, and had a normal neurological examination. Gait and balance were not altered. The wound was sutured. Complementary studies such as electrocardiogram and brain tomography were performed, with normal results. Vitals were stable.

Two days later, she asked for another consultation for she had to abandon acyclovir because of digestive intolerance (less than 3 days treatment). She was told to go on taking vitamin B pills as pain was still present. Less than a week later, she showed again at the ER for the pain, and told the assisting physician that she left pain killers afraid of adverse effects. Acetaminophen and tramadol were then prescribed emphasizing the concept of adherence. Again to the ER several days later, for persisting pain. Pregabaline was added to the previous indications, given in increasing dosages. This she took, however she had loose of balance and falls, so instead of pregabaline, gabapentine added to tramadol were

indicated. Digestive intolerance again, new consultation to the ER, her general practitioner, and a pain specialist. She did neither follow indication, nor the appointments taken. She went on asking for pain relievers, as the pain was interfering with her daily life. Different combination of pain killers and dosages were attempted, including hidrocoloid patches, benfotiamine, and amitryptiline, with poor response.

By January 2017, her general condition begun to brake, nothing was helping to ease the pain. She initiated a road to anxiety, fear, insomnia, and depression. She was brought to consultation to a psychiatrist were she was evaluated and given eszopiclone and lorazepam, finally in February (more than one year and a half apart from the initiation of the episode), she was rid of pain, and given citalopram for depression.

Case Report Number Two

Eighty one year old woman, heavy cigarette smoker, Type II Diabetes, dyslipidemia, glaucoma, anticoagulated for chronic atrial fibrillation. On October 2015, she suddenly felt an acute pain in her right eye ball. She asked for a consultation immediately, she was seen by two ophthalmologists, and given different eye drops. None helped. Only three days later some blisters appeared on the right forehead. She was then prescribed with oral Aciclovir 800 mg every 4 hours, 5 times daily, plus local Aciclovir cream, and non-steroidal painkillers.

The first eye examination showed: right bipalpebral edema, and blisters mostly on the upper eyelid. Slit-lamp examination: Right eye (RE): mild conjunctival congestion, no papillae, no secretion, transparent cornea with slight diffuse inferior perillimbicsuperficial punctate keratitis between hours 5 and 7. Intraocular pressure (IOP): RE: 18mmHg. Left eye (LE): 12mmHg.

She went on asking for consultation on a daily basis because of an unbearable pain, and was found to have a local infection, so she was prescribed oral Cephalosporin's, which she took for a week; and additional eye drops for her glaucoma (which got worse), eye tears, and local steroids. As the pain got worse, she also visited a healer and had Indian ink put on the crusts (three months after the beginning of the disease).

She also visited her physician, pain specialists and the emergency room for forty six times, till July 2017. Her complaining was always severe and incapacitating pain localized mainly within the eye and forehead. She was sequentially prescribed with oral non steroids, steroids, tramadol, gabapentin, carbamazepin, duloxetin, metadone, and all the possible combinations between them. She used virtually every pain killer available in our country. The pain got sometimes better, but is still on today, July 2017 (that is to say 22 months from the onset of the rash). Even these days, she still experiences severe pain which very much affects her life quality. She is still using medication and non pharmacological methods such as acupuncture and other techniques applied by healers.

Case Report Number Three

Seventy eight year old woman, with the history of Chronic Stable Angina, non-affiliated arrhythmia treated with amiodarone, swallowing disorders (bronchoaspiration, use of thickeners), hypothyroidism and depression treated with mirtazapine 15 mg a day.

In November 2014, she consulted the Emergency Department for an acute chest pain and blisters which begun less than one day earlier. She was diagnosed Herpes Zoster and prescribed with oral Acyclovir 800 mg every 4 hours, 5 times daily, as well as topic Acyclovir, and acetaminophen plus tramadol for the pain. One week later, and having finished oral Acyclovir, she asked for another consultation for the pain was not getting better. Pregabaline was added to the previous indications, given in increasing dosages in order to ease the pain. She also complained about pruritus. Paralellously her previous depression got worse as well as her insomnia, demanding a larger dose of mirtazapine. Three months after the beginning of the disease, she asked for consultation again with her GP. She was in great pain, as he had to abandon the painkillers because of digestive intolerance. Pregabaline was again initiated on a dosage of 25 mg three times daily, and also amitriptyline. Opioids were not re-indicated because of sickness. Pregabaline dosage was increased to 75 mg three times daily. Pain begun to slowly get better, and medications were well tolerated.

Six months after the initiation of HZ, she presented with falls, and had balance disturbances, which were attributed to pregabaline. Advice was given on fall prevention, but pregabaline remained the same, as pain was finally improving as well as her general status. Four months later, she was forced to abandon pregabaline and amitryptiline as falls and landing of balance advanced.

In November 2015 she begun to lose weight, balance problems and neuralgic pain got worse, as well as tolerance to medication. She was seen by Pain Specialists who presecribeda local cream with 50% glucose, 5% lidocaine and 40% dimetilsulfoxide (DMSO). This somehow improved pain tolerance during the day, but

worsened severely at night, interfering with sleep; so quetiapine was prescribed at night (12.5 mg). As pain and sleep disorders progressed, as well as her health condition worsened, she was put through new diagnostic tests. She was found to have anemia. Although she had had a video colonoscopy performed 5 years earlier which had only showed colon diverticulosis, her physician asked for blood tests, abdominal sonogram, and other tests which were initially normal, except for the anemia. Some changes were done in her medications: mirtazapine was replaced by venlafaxine, pregabaline was given at bed time, and intravenous iron was indicated. She did not improve, anemia increased, as well as pain, and weigh loss. By January she had already lost 8 kg in 5 months.

In February 2016 she presented with cachexia, and a urinary tract infection. Was admitted to hospital and other tests were performed. A double contrast CT scan showed an asymmetrical circumferential thickening of the descending colon suggestive of primary neoformative process. A left hemicolectomy was performed, despite what she died less than a month later.

Comments

Herpes Zoster is a self-limiting disease, characterized by a vesicular dermal eruption distributed in the region of a cutaneous dermatome, associated or not with neuropathic pain. It is caused by the reactivation of the Varicella Zoster Virus (VZV), which remains latent in the sensory ganglia of the spinal cord after suffering Varicella as a primary infection [1]. The condition occurs in all ages, but its incidence is highest among subjects who are in the sixth decade of life or beyond [2].

VZV belongs to Herpesviridae family, classified, in the subfamily Alfaherpesvirinae [5]. All these viruses share common features such as: having the ability to establish latent infection of neurons, producing recurrent disease in the corresponding dermatome, they are all heavily related to cell-mediated immunity, and produce characteristic vesicular lesions [3].

The risk of presenting HZ during life is 30% and up to 50% among people 85 years of age [4,5]. Immune changes at aging affect both innate immunity (decreased expression of the major histocompatibility complex type II), and adaptive immunity (reduced activation of CD4 + T cells against VZV, and decreased functioning of T lymphocytes. These changes cause a lower cellular immune response against VZV [6].

Symptoms

The first symptoms of HZ are usually pain and paresthesias in the affected dermatome. This usually precedes the eruption about 3 days, and varies from superficial itching, tingling or burning to deeper pain; some patients complain of a “nailed knife” feeling. The rash is almost always unilateral. In less than half of the cases there are general symptoms such as malaise, headache, photophobia and rarely fever [7].

The lesions begin as erythematous macules and papules, which become vesicles that appear in 12 to 24 hours, almost all are grouped in clusters on an erythematous basis. They follow the same trajectory as the pain. On day three, they evolve to pustules, dry and form crusts from day ten approximately, which may persist for 2 to 3 weeks. In normal individuals, new lesions continue to appear for 2 to 4 days, sometimes for up to 7 days. The virus can be recovered from the lesions for up to one week after the onset of the eruption. [8,9]. In most cases the diagnosis is clinical, although sometimes antigen detection techniques such as immunofluorescence, or detection of viral DNA by PCR [10].

Most Frequent Location

As in shown in our patient, the most frequent clinical form is intercostal, affecting one or two pairs of roots and intercostal nodes unilaterally. As regards the cranial nerves, the most frequently affected nerves belong to the trigeminal region, often with inflammation of the Gasser's ganglion. The ophthalmic branch is the most commonly affected. Ophthalmic herpes zoster is accompanied by pain in 93% of the patients, with a hight incidence of long lasting pain 31% of the cases, and even more, 71% of the cases in the older than 80 years [11].

Complications

Complications (cutaneous, visceral, neurological and ocular), occur as a result of failure in cell-mediated immunity. They may appear in 13-40% of cases and increase with age [12,13]. Neurological complications are the most serious, such as aseptic meningitis, meningoencephalitis, transverse myelitis, peripheral nerve palsy and vestibular dysfunction. Ocular complications are the second most frequent in the elderly.

Incidence, severity and presence of complications of the episodes, increase with age. It is estimated that 20% -

35% of people will develop HZ during their lifetime, with an incidence from 1.5 to 4.0 cases per 1000 people per year, peaking to 11 cases per 1000 people per year in their ninth decade of life [14]. Our working group found an incidence in elderly people in Argentina of 3.5 cases per 1000 people per year in the population between 60 and 64, to 6.6 cases per 1000 people per year in older than 85 years [15].

Post herpetic neuralgia (PHN), which, although is non-life threatening, may be associated with an important loss of autonomy, poorer quality of life, and significante costs. (See below)

Treatment

Acyclovir has been the antiviral most frequently used in the treatment of acute infection. The effectiveness of antiviral treatment is directly influenced by patient characteristics such as age, number of lesions, and severity of pain (null, mild, moderate or severe) and promptness of initiation of therapy [16]. Evidence suggests that treating patients with acyclovir within the first 72 hours of initiating the rash, presents significant benefits in terms of disease evolution and persistence of PHN [17].

It has been shown that patients treated with Acyclovir significantly shorten the healing time of HZ lesions with respect to the last new lesion in the affected dermatome, disappearance of the vesicles and formation of all crusted lesions. It also achieves maximum efficacy to decrease the severity of Post-herpetic neuralgia [18]. Valacyclovir is the L-valyl ester of Acyclovir. It is rapidly converted to Acyclovir after oral administration, resulting in serum concentrations 3 to 5 times higher than those achieved after oral administration of acyclovir. It has been shown that giving 1 g three times daily of Valaciclovir will produce the same results as 800 mg of acyclovir five times a day in immunocompetent persons at a more convenient dosage [19].

Famciclovir is the pro-drug diacetyl ester of 6-deoxypenciclovir, an acyclic analogue of guanosine. Following oral administration Famciclovir is rapidly converted through the first hepatic metabolism into penciclovir, a molecule that shares many characteristics with Acyclovir. The recommended dose for the treatment of shingles with Famciclovir is 500 mg every 8 hours for 7 days [20,22]. Famciclovir is not available in Argentina.

There are no contraindications to the use of these drugs in the elderly; however doses should always be adjusted according to the renal function calculated directly or indirectly.

Pain and HZ.Postherpetic neuralgia (PHN)

There are three phases of pain associated with herpes zoster:

1. Acute herpetic neuralgia refers to pain preceding or accompanying the eruption of rash that persists up to 30 days from its onset.
2. Sub acute herpetic neuralgia refers to pain that persists beyond healing of the rash but which resolves within less than two or three months of onset.
3. PHN refers to pain persisting beyond two or three months from the initial onset of the rash [23].

Neuralgic pain might develop before the rash, or during the acute phase of the disease. Typically 10% of those who experience acute pain will still have it at one month following the rash onset. Post-herpetic neuralgia (PHN) is a direct consequence of the damage caused by VZV on the peripheral nerve and one of the most frequent complications in the elderly [24].

In Argentina we followed 390 older adults after the acute HZ episode [15]. We found out that 40.6% were still in pain after the end of the episode. 27% patients had PHN with an average duration of 138.7 days (range 60 days to 24 months).

Post herpetic neuralgia is one of the most feared complications of shingles and can trigger disabling pain. It is not a continuation of acute herpes zoster but a complication of it.

It is important to discriminate acute pain and post herpetic neuralgia. The treatment of shingles pursues the prompt recovery of the patient and the prevention of PHN. The incidence of acute herpes zoster infection increases with impairment of the immune system due to age, disease, or chemotherapy. Among patients with acute herpes zoster infection, the major risk factors for PHN are older age, greater pain, and greater rash severity.

PHN is characterized by the presence of spontaneous or evoked pain, which may at the same time be constant or intermittent. Patients describe pain “like a sword”, intense and paroxysmal, that runs through the entire painful area in the form of a flashing sensation leaving the whole area hypersensitive and painful for minutes.
Sometimes subtle tactile or thermal stimulation may induce pain, unlike “normal” situations. This type of pain is called allodynia, and is frequently seen in PHN [25,26].

Sometimes pain may cause intense raveling in daily life, psychological well-being (depression, anxiety, fear, difficulty concentrating and enjoying life) and social interaction (recreational activities), Pain may also cause other conditions, such as fatigue, anorexia, decreased mobility and sleep disturbances.

In the patient described above, pain management was tough, it required several drugs, for a great amount of time (as it usually does), and was poorly tolerated, causing very much trouble in daily living, leading to anxiety and finally depression.

Some people may have a permanent feeling of dependency and not return to their previous lifestyle after the presentation of HZ, this may lead, in older adults, to daily dependency and finally frailty, as pain may last for months, and even years [27]. Long-term benefits of most therapies are uncertain, and side effects are common.

Elderly take often several medications, so drug/ drug interaction must be carefully examined. Besides, as pain in PHN may be chronic, long-term therapy is often required. The choice among treatments for PHN should be individualized according to patient-specific characteristics, comorbid conditions, medication side effect profile, and patient values and preferences. Randomized trials support the effectiveness of both topical and oral agents; however, PHN is very difficult and sometimes even impossible to treat despite the use of strong analgesics. Pathologic evidence suggests that VZV can cause permanent peripheral and central nervous system damage, destroying sites of intrinsic pain inhibitory mechanisms where analgesics act. That´s why patients respond poorly or are even almost refractory to all drugs for pain [28].

Although pain treatment, both acute and chronic, is beyond the intention of this manuscript, initial recommended treatment should include nonopioid agents, tricyclic antidepressants, gabapentin or pregabalin [29].

Herpes Zoster Prevention Life Attenuated Vaccine

The only well documented way to prevent both, HZ infection and the consequent development of PHN is now the live attenuated VZV vaccine. This vaccine reduces the incidence of HZ by 51% and the incidence of PHN by 66% [30,34]. Comparing 60 to 69 year old patients with 70 years old or older as receiving the vaccine, it seemed to be less effective in reducing the risk of HZ (63.9% versus 37.6% reduction), but conferred similar protection against PHN 65.7 in 60 to 69 versus 66.8% in 70 and older.

HZ vaccine became available in our country in 2014, and is recommended for immunocompetent adults aged 60 to 70. It has still low acceptance, perhapsdue to its cost, and because it has no health insurance covering.

As the possibility of a second episode is unlikely, and the indication of zoster vaccine should be considered at least one year after the previous episode and our patients were older than 80, we did not prescribe zoster immunization to the patients shown above.

Summary and Final Comments

As shown above, pain associated with HZ may be a long, and very much affecting of quality of life disease. Its treatment can present a challenge being that older adults are usually medicated with several drugs. So, drug interaction and dosage should be evaluated at all times when prescribing.

Our first case was difficult to manage because of medication intolerance, which is frequently found in older adults, and, as HZ is basically a disease that happens in older ages, this is a very frequent problem when treating this disease.

Our patients show how HZ and PHN led to difficulties in daily life activities, and in treatment management.

Education in the elderly and immunocompromised patients where HZ often occurs should be a medical goal, in order to make them understand the importance of early consultation and treatment.

As both HZ and PHN prevention are mainly achieved through the vaccine, which is recommended to individuals aged 60 to 70, independently of history of VZV infection, immunization should be offered to people without a recent episode of HZ. Because of antibody interference vaccine should be offered non before one year after HZ episode. In Argentina the vaccine became available by the end of 2014.

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