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CLINICAL CASE

Herpes Zoster Ophthalmicus presenting as acute headache

Debut de herpes zóster oftálmico como cefalea intensa

Sandra Marco Campos[a,b], Maria Teresa Tormo Alcañiz[a,c], Inmaculada Vilaplana Mora[a], Amadeo José Almiñana Almiñana[d], Carlos Miguel Angelats Romero[a]

[a]Servicio de Pediatría. Hospital Universitario Francisco de Borja. Gandía. Valencia, España.
[b]Centro de Salud de Carinyena. Vila-Real. Castellón, España.
[c]Instituto de Investigación Sanitaria. La Fe, Valencia, España.
[d]Servicio de Oftalmología. Hospital Universitario Francisco de Borja. Gandía. Valencia, España.

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What do we know about the subject matter of this study?

Herpes zoster ophthalmicus is uncommon in pediatric age, even more so in immunocompetent patients. Among other symptoms, it can produce acute headaches, so it should be assessed when making a differential diagnosis.

What does this study contribute to what is already known?

It highlights the importance of a complete anamnesis for any headache, especially if it is of recent onset or its characteristics have changed, as well as the need for clinical follow-up in a patient with herpes zoster ophthalmicus due to the appearance of possible complications.

Abstract

Herpes Zoster (HZ) is rare in childhood and is defined as the reactivation of the latent varicella-zoster virus in patients who have previously been infected with varicella. When the virus affects the ophthalmic nerve it is called herpes zoster ophthalmicus (HZO) and it can produce, among other symptoms, acute headache, so it must be considered as a differential diagnosis. **Objective:** To describe a clinical case of HZO in a pediatric patient and to recognize its clinical manifestations and their importance in the differential diagnosis of acute headache in children**. Clinical Case:** Immunocompetent 11-year-old girl, vaccinated according to the recommended immunization schedule, excluding chickenpox vaccine due to past infection, presented to the emergency department (ED) with a 5-day long unilateral headache. After 36 hours of hospitalization, she presented vesicular cutaneous lesions in her forehead, left upper eyelid, and nose. Positive fluorescein stain dendritic corneal lesions were identified in the ophthalmic exam. Antiviral systemic and topic therapy were set, obtaining an initial good response, but later she presented complications such as postherpetic neuralgia one month after hospital discharge and several postherpetic neuralgia episodes despite treatment with gabapentin in addition to two herpes zoster ophthalmicus relapses with acute keratouveitis one year after the initial episode. **Conclusion:** It is essential to include HZO in the differential diagnosis of acute headache,

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Correspondence:
Sandra Marco Campos
sandramarcocampos@gmail.com

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especially when presented unilaterally and/or with ocular symptoms, regardless of the presence of cutaneous lesions, and even more so in patients with history of chickenpox infection. Those patients who were vaccinated against this disease in their childhood will benefit from at least partial protection against HZO.

Introduction

Varicella-zoster virus (VZV) is a neurotropic human herpesvirus, which can cause two clinically distinct entities, the primary infection (varicella) and the reactivation (herpes zoster)[1,2].

The lifetime risk of herpes zoster (HZ) is 30%[1,3] and can occur both through reactivation of the wild-type virus and secondary to vaccination[4]. The attenuated virus in the varicella vaccine can produce a latent infection and reactivate[4,5,6]; however, the incidence of HZ in vaccinated children is lower due to the lower reactivation capacity of the vaccine virus[4,5,7].

After a primary infection, varicella-zoster virus is latent in the ganglia of the posterior spinal nerves and the sensory ganglia of the cranial nerves, such as the trigeminal nerve. Subsequently, it can reactivate, replicate, and migrate along a sensory nerve until it reaches the skin and tissues, where it produces the characteristic lesions of HZ[8]. The neuronal involvement produced by HZV in the affected sensory ganglia, spinal roots, and peripheral nerve could cause neuropathic pain before the appearance of the typical cutaneous manifestations[9]. The most frequently affected regions in HZ are the chest wall, ophthalmic branch of the trigeminal nerve, and lumbar and cervical regions[4,8].

Herpes zoster ophthalmicus (HZO) is characterized by the involvement of the ophthalmic branch of the trigeminal nerve (V1). It accounts for up to 20% of cases of HZ and its incidence increases with age, which is much more frequent in the sixth and seventh decade of life and exceptionally observed in the pediatric age[6,10,11,12]. Most of these cases are related to immunosuppression or varicella infection acquired in utero or during the first year of life[1,13], although it can also manifest in immunocompetent children[2,4,10,11].

The symptomatology of HZO in children is very similar to that of adults[4]. It can produce prodromal symptoms such as malaise, fever, lymphadenopathy, headache, photophobia, stabbing eye pain, etc., therefore, we should consider HZO as a differential diagnosis of acute headache[7,8,14,15,16]. This stage precedes the appearance of vesicular lesions although it may not be present in some cases, making the diagnosis more difficult[7,8,14,15,16].

The objective of this work is to describe a case of HZO in a pediatric patient, to recognize its clinical features, complications, and to emphasize the importance of the differential diagnosis of acute headaches in childhood.

Clinical Case

An 11-year-old female schoolchild consulted the emergency department due to 5-day history of left hemicranial headache. The pain was reported as stabbing, throbbing, severe, exacerbated by eye movements, with partial remission with first-level analgesia, and waking her up at night. She also presented photophobia, nausea, and vomiting.

As for her personal history, she had been vaccinated according to the Valencian Community vaccination schedule, however, she did not have the varicella vaccine and presented the disease at the age of 2, requiring outpatient care and symptomatic treatment.

At the first medical consultation, she presented with stable vital signs, intense pain affecting the general condition, mild conjunctival hyperemia, and left ocular lacrimation triggered by pain crises. No other pathological signs were found, and a complete neurological evaluation was performed without evidence of alterations.

Given the intensity of the pain, a blood test was performed, intravenous analgesia with metamizole and ketorolac was indicated, and the head CT scan showed no pathological findings. The Ophthalmology service also ruled out urgent pathology. She was admitted for observation and pain management.

Thirty-six hours after admission, with persistence of severe pain despite various treatments, vesicular lesions were observed on the forehead, palpebral area, and left nasal ala (figure 1), without affecting the nasal tip, suggesting a possible HZO. Given these new findings on the physical examination and the suspicion of a possible HZO, a new evaluation by Ophthalmology was requested, which confirmed the diagnosis by fluorescein eye stain showing dendritic lesions in the cornea. The complementary etiological study was extended, which subsequently confirmed the diagnosis of positive IgG antibodies for varicella-zoster virus (VZV) and VZV polymerase chain reaction in the vesicular exudate.

Treatment was started with oral acyclovir at 25mg/

kg/day divided into 5 doses and topical cream 3 times a day, which was maintained for 10 days, and intravenous methylprednisolone at 1 mg/kg/day was administered for 48 hours to manage pain and symptoms in the acute phase.

The patient initially evolved favorably, with the pain subsiding on the third day of admission. However, one month after hospital discharge, she consulted again due to an episode of left upper hemicranial pain, therefore, an ophthalmological examination was performed without pathological findings and, suspecting postherpetic neuralgia, treatment was started with gabapentin at 13 mg/Kg/day divided into 3 doses.

Subsequently, the patient presented a torpid evolution and suffered two episodes of acute keratitis and uveitis in the left eye and several crises of postherpetic pain despite treatment with gabapentin. In addition, she presented a new HZO relapse that was treated with oral valacyclovir 1g every 8 hours for a week and subsequently maintained at 500mg/8hs as prophylactic dose. In the second episode of HZO recurrence, autologous serum eye drops were also used as treatment along with the antiviral treatment described, administering 4 cycles of 5 days each.

The patient continued follow-up in the Neuropediatric, Ophthalmology, and Infectious Diseases services of a tertiary hospital.

Discussion

The dermatologic lesions of HZO present as a unilateral metameric rash, usually on the upper and lower eyelid and nasal areas. They usually appear 48-72 hours after the onset of pain, although they can appear up to one week after the onset of prodromal symptoms[7,8,9,9,14,16]. Initially, erythematous lesions appear, evolving into grouped papules and vesicles in the first 12-24 hours of evolution, followed by pustules and crusted lesions, usually resolving in 7-10 days[14]. The presence of lesions on the tip of the nose is known as Hutchinson's sign, and although this is very characteristic of HZO, it appears in only one-quarter of patients[14]. Ocular manifestations occur in up to 76% of cases[2], with keratitis, uveitis, and conjunctivitis as the most common, both due to direct virus invasion and secondary inflammation[17].

Up to 80% of patients with HZ suffer prodromal headache, malaise, or pain in the involved dermatome area that may occur several days before the onset of the characteristic rash[3,9]. This pain is characterized as sharp, stabbing, throbbing, burning, and that awakens at night[9]. Before the appearance of typical HZO lesions, it is difficult to orient the diagnosis or therapy and can be confused with migraines, tension headache, trigeminal neuralgia, or other pathologies[9]. Our patient presented directly with headache and severe orbital pain and did not present regional vesicular lesions until 7 days after the onset of these symptoms, which was a diagnostic challenge. Therefore, because of this case, we emphasize the importance of considering HZO as a differential diagnosis of acute headache, even in the pediatric age group, when the pain meets the characteristics described above and affects the dermatological area corresponding to the trigeminal nerve[18].

Postherpetic neuralgia is the most frequent complication of HZO in all age groups, affecting up to 20% of patients[3,7,19]. It is defined as persistent neuropathic pain localized in the affected dermatome 90 days after the onset of the rash[3,20,21]. The treatments of first choice are anticonvulsants such as gabapentin, pregabalin, or topiramate; and tricyclic antidepressants, such as amitriptyline, are also used in cases of moderate-severe pain that do not respond to or do not tolerate anticonvulsants[3,19,20]. In our case, the intense postherpetic neuralgia with partial response to treatment is striking, which is unusual in healthy pediatric patients, who generally have a good prognosis[2,13]. This may be related to the relative diagnostic and therapeutic delay, given the initial difficulty in identifying the cause of their

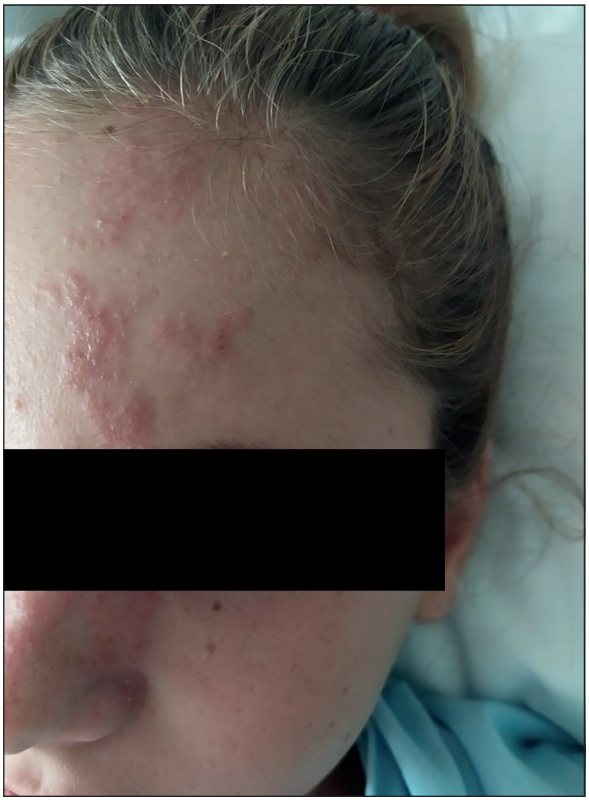

Figure 1. Herpetic lesions in the metameric area of the ophthalmic branch of the trigeminal nerve.

pathology due to the absence of dermatological lesions suggestive of HZO during the first days.

Today, we have the Zostavax® vaccine for HZO prevention and its main complication, postherpetic neuralgia. This is an attenuated vaccine, with characteristics similar to the varicella vaccine but with a lower potency. It is indicated for immunization of individuals 50 years of age or older. It should not be administered to immunocompromised patients, pregnant women, or those with a history of anaphylaxis to vaccine components. Currently, the safety and efficacy of Zostavax® in children and adolescents has not been established due to the lack of data. This vaccine has been shown to decrease the risk of developing HZO by up to 51.3% and has a 66.5% efficacy in preventing postherpetic neuralgia[14, 21].

Ocular complications of HZO occur in up to 50% of patients[3,6], with residual scarring in up to 15% of cases. The most frequent are pseudodendritic keratitis and punctate keratitis, which are evident during the eruptive phase of the disease[8,15]. Other possible ophthalmic complications are conjunctivitis, episcleritis/scleritis, iritis/uveitis, oculomotor nerve palsy, optic neuritis, or retinal necrosis, with potential compromise of visual acuity[8,15,20]. Our patient presented fluorescein-positive dendritic ocular lesions in the cornea, which initially resolved with antiviral treatment. She subsequently presented recurrences as acute keratouveitis twice, the first 12 months after the initial diagnosis and the second four months later. Both recurrences were treated with systemic antivirals and autologous serum, resolving without scar sequelae. The presence of recurrences is also an exceptional finding in healthy pediatric patients, which made us rule out immunosuppression in our patient.

Diagnosis is generally clinical, although there are complementary tests that can confirm it, such as the Tzanck smear test, biopsy, histopathological study, virus culture, molecular biology techniques, and serology; and in the case of HZO, the finding of epithelial keratitis with pseudodendritic lesions positive to fluorescein staining is very characteristic[16]. In our patient, clinical suspicion of HZO began with the appearance of cutaneous vesicles in the respective dermatome area and was subsequently confirmed with the ophthalmologic examination and especially with the positive PCR result for varicella-zoster virus in the exudate of the vesicular lesions, which is a very sensitive and rapid technique[13] that allowed starting treatment immediately.

The differential diagnosis should be made with HZ sine herpete, which consists of keratitis without the dermatologic lesions characteristic of HZO[14]; with herpetic keratitis caused by HSV-1[13], which frequently occurs in young patients; with vesicular skin lesions which, in this case, cover the dermatome area[17]; with impetigo[3,13]; and with "pseudodendritic" lesions due to epithelial toxicity associated with drugs and corneal abrasions[22]. In our case, the dermatologic lesions were located strictly in the dermatome area of the ophthalmic trigeminal root and therefore did not suggest pathology caused by the HSV. There was also no history of medication or use of cosmetics or other potentially harmful products, ruling out pseudodendritic lesions. Positive serology and PCR for varicella-zoster allowed establishing the final diagnosis of HZO.

The initiation of systemic and topical ophthalmic antiviral treatment within 72 hours from the onset of skin lesions reduces the incidence and intensity of ocular complications, and it should be maintained for 7-10 days[7,14]. The treatment of choice is oral acyclovir at 25 mg/kg/day divided into 5 doses (maximum 800 mg dose)[2,5,8,10,15]. Treatment with topical corticosteroid is controversial since it can be useful as an anti-inflammatory drug but it is difficult to discontinue its use without the reappearance of inflammatory signs[14]. In our case, antiviral treatment was started on the seventh day, when dermatologic and ophthalmologic lesions suggestive of HZ appeared, with a good initial response.

Systemic corticosteroids such as oral prednisone or intravenous methylprednisolone are indicated for the treatment of persistent pain in the acute phase and contribute to reducing skin lesions, facial paralysis, and ocular inflammation. They should always be administered associated with antiviral coverage[8,15,17]. In our patient, it was decided to associate intravenous methylprednisolone with antiviral treatment to optimize analgesia and inflammatory management in the acute phase, discontinuing it after the first 48 hours of treatment due to evident improvement.

Analgesics such as metamizole and paracetamol can be useful for the management of acute pain in pediatric patients, while NSAIDs are ineffective for the control of neuropathic pain[16]. Some patients present pruritus, so it may be necessary to add antihistamines. In our patient, she presented partial symptomatic relief with the administration of paracetamol and intravenous metamizole, with little response to NSAIDs.

Symptomatic treatment of skin lesions consists of drying them and applying antiseptics and local cold[8,17]. After the application of these measures in our patient, the lesions showed evident improvement, with rapid evolution to a crusty phase.

In the second ocular relapse of HZO, topical autologous serum drops were used as treatment. Autologous serum contains active factors such as growth factors, vitamin A, fibronectin, and antiproteases, which contribute to accelerating the healing of corneal surface alterations[23,24].

Regarding vaccination against varicella in chil-

dhood, there is evidence that patients who receive it have a lower incidence and milder forms of HZ, acquiring at least partial protection against HZO[13,14,15,25].

Conclusion

We present a case of HZO with acute headache at the onset in a previously healthy girl. We highlight the importance of including HZO in the differential diagnosis of acute headaches, especially in hemicranial presentations and/or with ocular symptoms regardless of the presence of associated skin lesions. Early diagnosis by ophthalmologic evaluation with fluorescein staining or by PCR of exudate from lesions if present is highly useful, even in early stages as early treatment with antivirals could prevent later complications such as visual acuity loss or postherpetic neuralgia. Our suspicion should be higher if the patient presents a history of varicella infection.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the parents (tutors) of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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