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Review article

Varicella-zoster virus vasculopathy. A review description of a new case with multifocal brain hemorrhage

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ABSTRACT

Background: The varicella zoster virus (VZV) is a highly neurotropic virus that, after the primary infection, remains latent in the nerve cells and can reactivate many years later, resulting in various conditions affecting the central nervous system, such as vasculopathy and stroke.
Methods: We report on a review of the published literature that included all case reports identified via PubMed and an additional unpublished case of VZV vasculopathy. All epidemiological, clinical, laboratory, imaging, virologic, treatment and outcome data collected are described.
Results: Of the 62 patients, 41.6% were immunocompromised. Ischemic stroke occurred in 77.2% of the patients, comprising cases of isolated (37.1%) and multifocal stroke (17.7%). Multifocal, ischemic and hemorrhagic stroke was only described in the newly reported case. The magnetic resonance imaging results were normal in 2.9% of the cases. The vascular studies (angiography and magnetic resonance angiography [MRA]) revealed signs of angiitis in 74.4% of the cases; the small arteries were involved in 38.5% of the cases, large arteries in 17.7% and mixed in 43.5%. For 95.2% of the patients, the cerebrospinal fluid (CSF) was positive for VZV IgG antibodies, and for 46.1% of the patients, the CSF was positive for polymerase chain reaction (PCR); however, the diagnosis was confirmed in only 3 of 6 biopsies.
Discussion: VZV vasculopathy can occur in both immunocompetent and immunosuppressed patients. Neuroimaging can reveal stroke and angiitis, and the detection of VZV-specific IgG antibodies in the CSF is a reliable and highly sensitive diagnostic tool. The multifocal nature of VZV vasculopathy makes biopsy a test with low sensitivity and high morbidity.

Contents

1. Introduction

The varicella zoster virus (VZV), which is part of the Herpesviridae family, is a highly neurotropic virus with a worldwide distribution. After the initial infection, which causes chickenpox in children, the virus remains latent within the neurons of the cranial nerves, dorsal

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roots and autonomic ganglia along the entire neuraxis [1–3]. In conditions of immunosuppression, including those attributable to age and stress, VZV can reactivate [1–3], usually as a rash (zoster). Occasionally, the immune response can prevent skin lesions but not viral replication in the dorsal root ganglia, with subsequent inflammation, necrosis and fibrosis of the ganglia. This can result in radicular pain with no skin lesions (*zoster sine herpete*) [2]. Less often, the virus can pass centripetally through the posterior roots and reach the central nervous system (CNS) [2,3]. VZV-induced CNS disease is extremely rare in immunocompetent patients. However, the difficult temporal–spatial association between zoster and the neurologic event, which sometimes precedes zoster by months with the appearance of neurological symptoms without any rash, results in this condition being underdiagnosed [4].

VZV vasculopathy is an uncommon manifestation of CNS disease caused by the direct viral invasion of cerebral arteries [5,6]. Although rare, VZV vasculopathy could be more common than previously supposed, given the fact that recent studies have demonstrated the increased risk of stroke in patients with a history of herpes zoster, especially within the first year after the rash [7,8]. Vasculopathy has traditionally been classified into 2 types: small-vessel disease with encephalopathy, occurring mainly in immunocompromised patients, and large-vessel disease characterized by contralateral hemiplegia following herpes zoster ophthalmicus (HZO), which has been predominantly observed in older individuals. However, recent reports have suggested a multifocal condition, with involvement of both large and small vessels [4]. It has been hypothesized that the virus remains latent in the trigeminal ganglia until reactivation, when the virus spreads transaxonally to infect the adventitia where the disease begins [2,5,6]. However, VZV vasculopathy is not yet completely understood, and most of the related literature is based on individual case reports. A better characterization of this disease is therefore necessary.

2. Methods

We report a new case and conduct a review of the literature published up to February 2013, including all case reports identified via PubMed using the keywords “VZV vasculopathy”, “herpes zoster ophthalmicus” and “contralateral hemiplegia”. Case reports cited in the collected articles were added to the list. Articles written in English, French, German or Spanish were included. We included all epidemiological, clinical, imaging, treatment, outcome and cerebral spinal fluid (CSF) abnormality, data from each patient with a definitive diagnosis of VZV vasculopathy obtained by isolated immunoglobulin G (IgG), polymerase chain reaction (PCR), both IgG and PCR or by other methods. We excluded patients who had incomplete medical histories and those of pediatric age. Given that this was a review of published literature, there was no requirement for an ethics board approval. Our patient signed an informed consent for publication.

Based on brain imaging (and on vascular studies for many of the cases), arterial disease was classified as large artery, small artery or mixed. Large artery included internal and external carotid arteries, the anterior cerebral arteries and their major branches (e.g., the pericallosal and callosal marginal arteries), the middle cerebral arteries and their major branches, the posterior cerebral arteries, the basilar artery, vertebral arteries and the anterior and posterior inferior cerebellar arteries. In contrast, diseases of the penetrating arteries supplying the deep-seated structures (thalamus and brainstem) were considered small artery diseases.

3. Results

3.1. Case report

A 45-year-old Ecuadorian-born immunocompetent woman, who had been living in Spain for the last 14 years, presented abrupt onset of headache and hemianopia at the time of diagnosis. Her past medical history included iron deficiency anemia and a diagnosis of internal hemorrhoids by panendoscopy. The patient reported no drug or toxic substance consumption but had a family history of gastric cancer. The patient was admitted to the emergency department with severe holocranial headache, nausea and vomiting and decreased visual acuity lasting 3 days. The examination revealed a raised nevus of 0.5 cm, with no clear signs of malignancy and aortic systolic murmur, grade II/IV. The neurological examination revealed only a left homonymous hemianopia. An emergency cranial computed tomography (CT) showed a multifocal intraparenchymal hemorrhage in the occipital and right parietal lobes associated with a left frontal subarachnoid hemorrhage (SAH) (Fig. 1A–B). Due to suspected metastatic lesions, the patient was admitted to the internal medicine ward for primary tumor screening. Magnetic resonance imaging (MRI) with an angiographic sequence showed a right hemisphere hematoma with mass effect, SAH and subdural hematoma. The results of the autoimmune panel (antinuclear antibodies, anti-DNA, anti-Smith, antineutrophil cytoplasmic antibodies, anti-ribonucleoprotein, anti-Ro, anti-La, cryoglobulins and anticardiolipin), tumor markers and plasma serology (human immunodeficiency virus, hepatitis B and C virus, viral hemorrhagic septicemia, cytomegalovirus, Epstein–Barr virus, VZV, *Treponema pallidum*, *Brucella* and *Rickettsia conorii*) were negative. Notably, the patient was VZV IgG positive in a serum sample. The results of the body CT scan, transthoracic echocardiography, mammography, thyroid ultrasound and skin lesion biopsy were normal. A PET scan revealed a metabolic increase in the gastric wall and anal canal. The study was therefore completed by echo-endoscopy and biopsies, which indicated a pattern of chronic gastritis confirmed by histology. Colonoscopy confirmed the diagnosis of internal hemorrhoids. On the 11th day of hospitalization, the patient developed right brachiocrural hemiparesis and a new ischemic lesion in the left parietal border-zone, which was revealed by MRI (Fig. 1C). A brain biopsy was performed, but no tumor cells or signs of angiitis were observed. On the 13th day postadmission, a thoracic vesicular rash compatible with zoster was diagnosed, and treatment with intravenous acyclovir was started. The neurologist was then consulted who suggested an angiography, which revealed multiple areas of narrowing and beading in small-to-medium vessels of anterior and posterior circulations (Fig. 1D–E). The cerebrospinal fluid (CSF) presented mild hyperproteinemia, with normal cells and glucose levels. The CSF albumin/plasma ratio was 5.5, with an IgG index of 0.52 indicating integrity of the blood–brain barrier (BBB). PCR analysis revealed no amplifiable VZV DNA, but the analysis of anti-VZV IgG antibodies was positive. Due to the patient's improved conditions following zoster treatment, the acyclovir treatment was not repeated. A new MRI 2 months after admission showed decreased hemorrhagic lesions. The follow-up angiography showed an improvement of the vasculopathy, although some areas of stenosis still remained. The patient was eventually discharged with a National Institutes of Health Stroke Scale score of 2, with subsequent follow-up at the outpatient clinic.

3.2. Review

In the 39 articles reviewed, we identified 62 patients with a clinical diagnosis consistent with VZV vasculopathy [4,9–47]; 39 cases were excluded due to the lack a definitive microbiological diagnosis. The frequencies and epidemiological, clinical, diagnostic, treatment and outcome characteristics of the patients with VZV vasculopathy are summarized in Table 1, and detailed information of each case is reported in the Appendix (online only).

The mean age of the selected group of patients was 55 years, ranging from 18 to 88 years, and there were no significant differences between genders. CNS disease caused by VZV has traditionally been thought to be more frequent when immunity (especially the cellular-mediated response) deteriorates, for example with age or disease [2]. However, in the reviewed cases, only 41.9% (26/62) of the patients were immunosuppressed and 50% were older than 55 years. Up to 58.1% of the