Acute varicella zoster encephalitis without evidence of primary vasculopathy in a case-series of 20 patients

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Abstract

Varicella zoster virus (VZV) is a leading cause of acute viral encephalitis but little is known about its clinical, biological and imaging features. Furthermore, the most favourable treatment regimen has not been determined. We studied a prospective cohort of 20 HIV-negative patients presenting with acute VZV encephalitis caused by primary infection or reactivation. VZV was identified in 16 of 20 cases by PCR detection of the DNA in the cerebrospinal fluid. The four remaining cases occurred during or soon after a VZV rash. The median age of the 17 adults was 76 (19–86) years; the three other patients were children (0.5–5 years). Three patients were immunocompromised. Nine adult patients presented with a rash. Eighteen patients presented with fever and an acute encephalitic syndrome: diffuse brain dysfunction, focal neurological signs, seizures and cranial nerve palsies. Three patients presented with either ventricular or subdural haemorrhage, one with myelitis, and one with asymptomatic stenosis of the middle cerebral artery. The imaging was either normal or revealed non-specific abnormalities such as cortical atrophy but no evidence of stroke. All patients were given acyclovir at various dosages and durations but the case fatality rate remained high (15%) and sequelae were frequently observed either at discharge or at follow-up 3 years later.

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Introduction

Varicella zoster virus (VZV) is a virus of the *Alphaherpesvirinae* subfamily, responsible for human infections with various clinical presentations. Primary infection occurs most frequently during childhood and presents as varicella; it is followed by long-lasting viral latency in the spinal and cranial ganglia [1,2]. This infection is common, affecting almost all non-vaccinated children. Infection reactivation occurs mainly in immunocompromised or elderly patients. The most frequent presentation in adults is herpes zoster (shingles), with an estimated annual incidence of 1.2–5.2 cases/1000 [2]. Post-herpetic neuralgia is a frequent complication in elderly patients [3].

Neurological complications caused by varicella can involve peripheral or central nervous system. They include cerebellitis, meningitis, myelitis, optic neuritis, polyneuropathy, acute encephalitis and vasculopathy [2,4]. Some neurological presentations can also appear with, precede, or follow herpes zoster: sensory or motor peripheral paralysis, isolated and multiple cranial nerve palsies including ophthalmoplegia and the Ramsay Hunt syndrome, myelitis, encephalitis, vasculopathy and cerebellar ataxia [5]. Neurological symptoms caused by VZV infection can also occur without any cutaneous rash (zoster *sine herpete*) and the detection of DNA or specific

VZV antibodies in the cerebrospinal fluid (CSF) is here the only proof of VZV involvement [5].

Several mechanisms explain the occurrence of neurological signs after VZV infection: parenchymatous encephalitis (with or without demyelination), microglial influx, granulomatous and large vessel vasculopathy inducing strokes (grossly transient cerebral arteriopathy in children and delayed contralateral hemiparesis of zoster ophthalmicus in the elderly), meningitis or necrotizing myelitis [6,7]. Subacute or chronic VZV encephalitis are encountered in immunocompromised patients as the result of small vessel vasculopathy and glial infection inducing leukoencephalitis. Myelitis, large vessel involvement and ventriculitis have also been reported [7,8]. Acute ataxia in children and vasculopathies in adults are the most frequently cited neurological complications of VZV infection [5,9,10]. In contrast, acute encephalitis *sensu stricto* has rarely been reported [11–14] and even fewer reports have been published describing the clinical features and follow-up of these patients [15–18]. The importance of VZV in the epidemiology of acute encephalitis in the general population has been highlighted in multicentre prospective studies [11–13].

We report the clinical features of patients with VZV encephalitis enrolled in a prospective multicentre study in France, in 2007.

Methods

A case-patient with acute encephalitis was a patient 28 days of age or older hospitalized in mainland France in 2007, with (i) an acute onset of illness; (ii) at least one abnormality of CSF (white blood cell count ≥4 cells/mm^3 or protein level ≥40 mg/dL); (iii) fever or recent history of fever ≥38°C; and (iv) decreased consciousness, or seizures, or altered mental status, or focal neurological signs. HIV infection was an exclusion criterion. Aetiological investigation of enrolled patients was described previously [11].

A confirmed case of VZV encephalitis was a case-patient with VZV DNA detected in the CSF by PCR. A possible case of VZV encephalitis was a case-patient with encephalitis occurring simultaneously or shortly after varicella or herpes zoster without biological confirmation of VZV infection, and with other possible aetiologies of encephalitis excluded by the investigation. Clinical and biological data were collected using a standardized questionnaire and the results of electroencephalography examinations were recorded. A single expert (TdB) reviewed all available magnetic resonance and computed tomography images to assess brain lesions.

The outcome of VZV patients was assessed 3 years after discharge using the Glasgow outcome scale [19].

Informed written consent was obtained from all patients or from their parents for children aged <18 years. The study was approved by the ethics committee of Grenoble (No. 172003).

Results

Demography

Twenty of 253 (8%) case-patients enrolled in the initial study were VZV patients [11]. Sixteen were confirmed cases and four were possible cases (Table 1). Two possible cases were 5-year-old boys with negative VZV CSF PCR on admission and no further CSF testing. They presented with varicella, respectively, 1 day and 1 week before the onset of neurological symptoms. The two other possible cases were adults (76 and 78 years of age) presenting with radicular zoster (one spinal, one ophthalmicus) 3 days and 3 weeks, respectively, before the onset of neurological symptoms.

The male to female ratio was 3. Three patients were children (the two 5-year-old boys mentioned above and a 6-month old boy). The distribution of age among adult patients was bimodal with three young adults (19, 20 and 26 years old) and 11 people ≥75 years old (median 76 years old, range 19–86 years). None of the VZV patients had ever been vaccinated against VZV.

Clinical features

Ten (50%) patients (nine adults and one child) had comorbidities, three of which could be considered immunosuppressive conditions: osteosarcoma, recent heart–lung transplant and systemic lupus erythematosus with long-term corticosteroid treatment (Table 1).

Eleven VZV patients (55%) had a rash before hospitalization: zoster in eight adults and varicella in three children, of whom two (a child and an adult) no longer had cutaneous signs on admission.

The symptoms of the VZV patients on admission are presented by frequency in Table 2. Six patients (30%) required admission to intensive care units, four were mechanically ventilated. The most frequent neurological symptoms were disorientation and confusion (70%), meningeal signs (60%), focal neurological signs (55%) and apathy (50%). Cranial nerve palsy was present in eight patients (40%), namely central facial nerve paralysis in seven cases and oculomotor nerve paralysis in one case.

Lumbar puncture was performed before day 2 of hospitalization in 80% of cases and before day 4 in 95%. The