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SHORT COMMUNICATION

Central nervous system infections caused by varicella-zoster virus

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Abstract We carried out a clinical and epidemiological study of adult patients with varicella-zoster virus central nervous system infection diagnosed by PCR in cerebrospinal fluid. Twenty-six patients were included. Twelve (46.2 %) patients were diagnosed with meningitis and fourteen (53.8 %) with meningoencephalitis. Twelve (46.2 %) had cranial nerves involvement (mainly the facial (VII) and vestibulocochlear (VIII) nerves), six (23.1 %) had cerebellar involvement, fourteen (53.8 %) had rash, and four (15.4 %) developed Ramsay Hunt syndrome. Three (11.5 %) patients had sequelae. Length of stay was significantly lower in patients diagnosed with meningitis and treatment with acyclovir was more frequent in patients diagnosed with meningoencephalitis. We believe routine detection of varicella-zoster virus, regardless of the presence of rash, is important because the patient may benefit from a different clinical management.

Keywords Varicella-zoster virus · Meningitis · Meningoencephalitis · Cerebellitis · Ramsay Hunt syndrome

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Introduction

Varicella-zoster virus (VZV) causes a wide variety of neurological syndromes both during primary infection and after reactivation from latency (Gnann and Whitley 2002). The infection can affect central and peripheral nervous system causing meningitis, encephalitis, cerebellar ataxia, VZV vasculopathy and myelopathy among others. The non-specificity of signs and symptoms makes more difficult the clinical suspicion, particularly in absence of rash (Gilden et al. 2010). The use of the polymerase chain reaction (PCR) in the diagnosis is helping to a better understanding of the different neurological syndromes produced by this virus. This study aimed to describe the epidemiology and clinical presentation of the VZV central nervous system (CNS) infection.

Material and methods

This retrospective clinical-epidemiological descriptive study of all patients older than 14 years diagnosed with VZV CNS infection attending the referral hospital on the island of Gran Canaria (population of 335,000 adults) was performed between January 2001 and June 2014.

Cerebrospinal fluid (CSF) samples from patients with neurological signs and symptoms, pleocytosis (>5 white cells/μl) or radiological or electroencephalographic abnormalities were examined by amplification of VZV DNA by PCR using two

commercially kits (Herplex® or CLART® ENTHERPEX, Genomica S.A.U. and LightCycler® VZV Qualitative kit, Roche Molecular Diagnostics). Medical records were reviewed and epidemiological data, clinical manifestations, laboratory tests, neuroimaging tests, treatment and outcome were collected. Acute meningitis is a syndrome characterized by the presence of fever or headache and pleocytosis and meningoencephalitis is further characterized by an acute confusional state or the presence of focal neurological deficit.

Statistical analysis was performed using SPSS Statistics v. 18.0. The Mann-Whitney *U* test was used to compare differences between means. The chi square test or Fisher's exact test was used to evaluate a relationship between two categorical variables. *P* values ≤0.05 were considered statistically significant. The Bioethics Committee of the Hospital approved the study.

Results

Twenty-six patients had detectable VZV DNA in CSF. Seventeen (65.4 %) patients were male and the median age was 55 years (range 15–88 years). The average annual incidence of VZV CNS infection during the study period was 0.58 ± 0.60 cases per 100,000 inhabitants. Four (15.4 %) patients were immunosuppressed (three with autoimmune diseases and one with multiple myeloma). Twelve (46.2 %) cases were diagnosed with acute meningitis and 14 (53,8 %) with meningoencephalitis. Twelve (46.2 %) patients had also cranial nerve involvement, six (23.1 %) had cerebellar involvement and one (3.8 %) had spinal cord involvement. Fourteen (53.8 %) patients had a rash (13 had herpes zoster and one had chicken pox). The median time from onset of symptoms to CSF sample collection was 4 days (range 1–15).

Table 1 shows the clinical and epidemiological features of patients. Of patients with acute meningitis, one (8.3 %) was immunocompromised and five (41.7 %) had cranial nerve involvement. The facial nerve was affected in three patients, the abducens nerve in one patient and the vestibulocochlear nerve in another patient. Ten (83.3 %) patients had full recovery and two had sequelae 6 months after the onset of symptoms (one tension-type headache and other gait instability), neither had been treated with acyclovir.

Of patients with meningoencephalitis, three (21.4 %) were immunocompromised and six (42.9 %) had cerebellar ataxia, in three cases associated with Ramsay Hunt syndrome (RHS). Seven (50.0 %) patients had cranial nerve involvement. The facial nerve was affected in three patients, the vestibulocochlear nerve in three other patients and the facial and vestibulocochlear nerves in one patient. Five (35.7 %) patients showed large-vessel vasculopathy in neuroimaging studies. One patient with RHS, who received treatment with acyclovir 9 days after onset the symptoms, had sequelae 6 months after.

Patients with acute meningitis had lower median age compared to patients with meningoencephalitis (38.2 ± 17.6 versus 65.7 ± 16.7 years; $p \leq 0.01$) and the presence of rash was less frequent (25 versus 78.6 %; $p \leq 0.05$). Treatment with acyclovir was more frequent in patients with meningoencephalitis (85.7 versus 41.7 % $p \leq 0.05$) and the duration of hospitalization was longer (16.8 ± 12.6 versus 6.9 ± 7 5 days; $p \leq 0.05$) in these patients.

Discussion

This study describes a serie of cases of VZV CNS infection in adults, which affected patients of all ages and that was expressed with a wide variety of symptoms, both in the presence and absence of rash.

Acute meningitis and meningoencephalitis were the most frequent syndromes. The median age was below 60 years, but patients with meningoencephalitis were significantly older than those with meningitis (difference not previously described) and over 80 % of patients were immunocompetent, similar to other studies (Lozano Becerra et al. 2013; Persson et al. 2009; Pollak et al. 2012). Up to 23 % of patients had also cerebellar involvement, a complication typically associated with VZV primary infection in children. Another clinical finding included the cranial nerve involvement that has been described in other series (Pahud et al. 2011; Persson et al. 2009), although at a percentage lower than ours (46.2 %). The most commonly involved cranial nerves were the seventh causing facial paralysis and eighth causing nystagmus and hearing loss.

In the last few years, the neurological involvement without rash has been frequently described (Lozano Becerra et al. 2013; Pahud et al. 2011; Persson et al. 2009). Only 53.8 % of patients in our study had rash and their presence was significantly higher in meningoencephalitis. Because of this, the presence of rash is a poor marker of suspicion of VZV infection, especially in patients with meningitis. Due to meningitis is a less severe syndrome, affects immunocompetent younger patients and rash is not present in a high percentage of cases, it could cause low suspicion and lead to an underdiagnosis of this infection.

As previously described, the outcome of patients with meningoencephalitis was often less favorable than those with meningitis (Persson et al. 2009; Science et al. 2014; Grahn et al. 2013), but we did not observe differences. About 40 % of our patients with meningitis and 85 % of patients with meningoencephalitis were treated with

Table 1 Clinical and epidemiological features of patients with meningitis and meningoencephalitis caused by VZV

	Overall ($n = 26$)	Meningitis ($n = 12$)	Meningoencephalitis ($n = 14$)
Epidemiological features			
Age (years), median (IQR)	55 (37.5)	37.5 (26.7)	71.5 (17.5)
Male, *n* (%)	17 (65.4)	8 (66.7)	9 (64.3)
Immunosuppression, *n* (%)	4 (15.4)	1 (8.3)	3 (21.4)
Symptoms (%)			
Headache	20 (76.9)	12 (100)	8 (57.1)
Fever	15 (57.7)	8 (66.7)	7 (50.0)
Vomiting	15 (57.7)	6 (50.0)	9 (64.3)
Rash	14 (53.8)	3 (25.0)	11 (78.6)
Acute confusional syndrome	11 (42.3)	0 (0.0)	11 (78.6)
Staff neck	10 (38.5)	5 (41.7)	5 (35.7)
Hemiparesis	9 (34.6)	3 (25.0)	6 (42.9)
Somnolence	8 (30.8)	0 (0.0)	8 (57.1)
Personality change	7 (26.9)	0 (0.0)	7 (50.0)
Ataxia	7 (26.9)	1 (8.3)	6 (42.9)
Cerebellitis	6 (23.1)	0 (0.0)	6 (42.9)
Aphasia	5 (19.2)	1 (8.3)	4 (28.6)
Dizziness	4 (15.4)	1 (8.3)	3 (21.4)
Nistagmus	4 (15.4)	1 (8.3)	3 (21.4)
Ramsay Hunt syndrome	4 (15.4)	0 (0.0)	4 (28.6)
Hearing loss	3 (11.5)	0 (0.0)	3 (21.4)
Seizures	2 (7.7)	0 (0.0)	2 (14.3)
Tinnitus	1 (3.8)	0 (0.0)	1 (7.1)
Cranial nerve involvement, *n* (%)	12 (46.2)	5 (41.7)	7 (50.0)
CSF features, median (IQR)			
Leukocytes (per μl)	122 (198.3)	127.5 (369.7)	121 (170)
Proteins (mg/dl)	82 (90.6)	90.7 (39.5)	71.9 (155.1)
Treatment with acyclovir			
Patients, *n* (%)	17 (65.4)	5 (41.7)	12 (85.7)
Time, median (IQR)	10 (9.5)	10 (5.5)	14 (12.5)
Length of stay (days), median (IQR)	10 (16.5)	3,5 (12.4)	11 (21.2)
Sequelae, *n* (%)	3 (11.5)	2 (16.7)	1 (7.1)

n number, *IQR* interquartile range

acyclovir. Treatment with acyclovir reduces the duration of symptoms (Gnann and Whitley 2002) and also it had been described as a good prognostic factor in the complete recovery of patients with RHS (Murakami et al. 1997) as in untreated patients only about 20 % of them recovered completely (Peitersen 2002). None of the untreated patients with meningoencephalitis had sequelae, and the only patient with sequelae was treated with acyclovir, although there was a delay at the start of therapy. Two of seven patients with untreated meningitis had sequelae. Most studies report the presence of sequelae, although they did not often assesses the features that may explain the appearance of the same. Furthermore they did not analyze whether these are related to the nature of the infection, with no introduction of a treatment or a combination of both. It would be interesting to analyze in further studies, the presence of sequelae in untreated patients.

Because of the wide variety of symptoms caused by VZV, it should be made more prospective descriptive studies that detail and analyze not only the clinical presentation, but also the progress and the sequelae. Further studies would be required to establish whether the introduction of a specific treatment with acyclovir is effective, especially in severe cases. We believe important to include VZV routine detection in all neurological infections of possible viral etiology, regardless of the severity of symptoms and the presence of rash.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

References

Gilden D, Cohrs RJ, Mahalingam R, Nagel MA (2010) Neurological disease produced by varicella zoster virus reactivation without rash. Curr Top Microbiol Immunol 342:243–253. doi:10.1007/82_2009_3

Gnann JW Jr, Whitley RJ (2002) Clinical practice. Herpes zoster. N Eng J Med 347:340–346. doi:10.1056/NEJMcp013211

Grahn A, Hagberg L, Nilsson S, Blennow K, Zetterberg H, Studahl M (2013) Cerebrospinal fluid biomarkers in patients with varicella-zoster virus CNS infections. J Neurol 260:1813–1821. doi:10.1007/s00415-013-6883-5

Lozano Becerra JC, Sieber R, Gladys M, Tschuor CS, Meylan P, Bernasconi E (2013) Infection of the central nervous system caused by varicella zoster virus reactivation: a retrospective case series study. Int J Infect Dis 17:e529–e534. doi:10.1016/j.ijid.2013.01.031

Murakami S, Hato N, Hourichi J, Honda N, Gyo K, Yanagihara N (1997) Treatment of Ramsay Hunt syndrome with acyclovir-prednisone: significance of early diagnosis and treatment. Ann Neurol 41:353–357. doi:10.1002/ana.410410310

Pahud BA, Glaser CA, Dekker CL, Arvin AM, Scott SD (2011) Varicella zoster disease of the central nervous system: epidemiological, clinical, and laboratory features 10 years after the introduction of the varicella vaccine. J Infect Dis 203:316–323. doi:10.1093/infdis/jiq066

Peitersen E (2002) Bell's palsy: the spontaneous course of 2,500 peripheral facial nerve palsies of different etiologies. Acta Otolaryngol Suppl 549:4–30

Persson A, Bergström T, Lindh M, Namvar L, Studahl M (2009) Varicella-zoster virus CNS disease-viral load, clinical manifestations and sequels. J Clin Virol 46:249–253. doi:10.1080/00016480232040169 4

Pollak L, Dovrat S, Book M, Mendelson E, Weinberger M (2012) Varicella zoster vs. herpes simplex meningoencephalitis in the PCR era. A single center study. J Neurol Sci 314:29–36. doi:10.1016/j.jns.2011.11.004

Science M, MacGregor D, Richardson SE, Mahant S, Tran D, Bitnum A (2014) Central nervous system complications of varicella-zoster virus. J Pediatr 165:779–785. doi:10.1016/j.jpeds.2014.06.014