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Long-term outcomes of varicella zoster virus infection-related myelitis in 10 immunocompetent patients

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ABSTRACT

Objective: To describe the clinical presentation and long-term disease outcomes of varicella zoster virus (VZV) infection–related myelitis (VZVM) in immunocompetent patients.
Method: A series of 10 immunocompetent patients with VZVM were retrospectively observed and followed (3–96 months).
Results: The onset of myelitis was timed in relation to the appearance of VZV-associated rash (−3 to 50 days). Rash locations included the cervical (5), thoracic (2), and lumbar (3) dermatomes, whereas myelitis localized to the cervical (6) and thoracic (9) spinal cord and the medulla (1). Spinal MRI revealed extensive longitudinal transverse myelitis in nine patients, with multiple segmental lesions (≥2 segments) evident in five patients. Aquaporin-4, myelin oligodendrocyte glycoprotein, ganglioside Q1b, and ganglioside T1b antibodies were detected in some patients. Three patients fulfilled the 2015 diagnostic criteria for neuromyelitis optica spectrum disease, of whom two relapsed. Seven patients were treated with intravenous antivirals and methylprednisolone, with the remaining three patients receiving methylprednisolone only. Ongoing immunosuppressive therapy was provided for two patients who experienced relapses. To date, no patients have reported VZV reactivation. Over the course of follow-up, the Expanded Disability Status Scale (EDSS) score deceased from 4.9 to 2.6 on average.
Conclusions: VZVM runs a relatively benign course in immunocompetent patients, although relapses can occur depending on patient immune status. A comprehensive evaluation of patient's autoimmune condition is recommended.

1. Introduction

Infectious diseases are responsible for 20% to 40% of all cases of transverse myelitis, of which varicella zoster virus (VZV) is the most common viral infection (Sellner et al., 2010). Recently, some suggested immuno-suppression after varicella zoster virus infection-related myelitis (VZVM) to avoid relapse. In combination with antibodies against aquaporin-4 (AQP4) detected in the VZVM, these observations have raised considerable debate regarding the relationship between VZVM and neuromyelitis optica spectrum disorders (NMOSD) (Heerlein et al., 2009; Machado et al., 2015; Park et al., 2013) although a definitive link remains elusive.

Much of the literature surrounding VZVM exists in the form of case reports that provide little insight into the mechanisms underlying the onset of VZVM and its prognosis. This severely limits their utility in a clinical setting. Important treatment decisions, such as whether to use methylprednisolone at high doses to relieve autoimmune inflammation or low doses to inhibit inflammation caused by viral infection, are typically made on a case-by-case basis, with few standards available to predict treatment outcomes. A better understanding of the factors influencing disease outcomes in VZVM, such as a patient's immune status, is therefore necessary.

In this study, we retrospectively observed 10 immunocompetent patients diagnosed with VZVM in our department from 2007 to 2017. Then we followed patients to assess their current health conditions and analyzed data on each patient's clinical features, disease course, magnetic resonance imaging (MRI) results, cerebrospinal fluid (CSF) findings, treatments, and relapse characteristics. These data were used to better understand the disease progression and to propose a strategy for therapeutic management of VZVM.

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Table 1
General conditions of the patients.

	sex	Age	IT (day)	Season	TOP (day)	EDSS score	PMNI	Medical history	Treatment	Complications	Intervals (month)
						Onset/follow					Onset/follow
1	M	76	−3[a]	Autumn 2009	13	6.5/3.5	NP	CVD, CB, ICVD, Prostatitis	Tapering M + A	Acute renal failure	96
2	F	52	50	Winter 2014	3	4.5/3.0	NP	Healthy	Tapering M	No	45
3	F	42	1	Autumn 2014	12	6.0/1.0	negtive	Hysterectomy	M[a] + GG + MM	No	33
4	F	54	14	Summer 2014	5	6.5/2.5	NP	Healthy	Tapering M + GG + A + MM	Lower extremity thrombus	38
5	M	56	1	Summer 2016	5	7.0/1.5	positive	DM, Cataract	Tapering M + A	Depression	13
6	M	57	32	Autumn 2016	13	2.5/1.5	negtive	HT, DM, Cholecystectomy	Tapering M + A	Omarthritis and carpitis	12
7	F	59	15	Autumn 2016	3	2.0/1.0	NP	HT, Ovariotomy	Tapering M + A	Drug-induced liver injury	11
8	M	80	30	Summer 2017	11	9.0/8.5	positive	HT, Appendectomy	Tapering M + A	No	3
9	F	74	9	Summer 2017	20	3.0/2.0	negtive	DM, ICVD	Tapering M + A	No	3
10	M	31	30	Summer 2017	5	1.5/1.5	NP	Healthy	Tapering M[a]	No	3

IT: interval time between rash and myelitis. TOP: times from the onset to the peak of symptom (EDSS score arrives the highest). PMNI: peripheral motor nerve injury proved by EMG. NP: the EMG is not performed. CVD: cardiovascular disease. CB: chronic bronchitis. ICVD: ischemic cerebral vascular disease. DM: diabetes mellitus. HT: hypertension. M: methylprednisolone. A: aciclovir. GG: gamma globulin. MM: mycophenolatemofetil.

[a] Means oral.

2. Methods

To identify cases of VZVM, we performed an initial screening of our institute's medical records for patients diagnosed with VZVM between 2007 and 2017 using the keywords *neuromyelitis, myelitis, longitudinally extensive transverse myelitis, opticospinal MS, neuromyelitis optica, neuromyelitis optica spectrum disorders,* and *varicella zoster virus infection.* Then we screened potential cases to confirm immunocompetence and to exclude myelopathies caused by other reasons. VZVM diagnosis was based on the appearance of a rash closely followed by the onset of myelitis. VZV infection was confirmed based on laboratory findings, including increased VZV immunoglobulin G (IgG), or detection of VZV DNA in the cerebrospinal fluid (Hung et al., 2012). All patients were followed at the time of this study. Patient data were analyzed for clinical features, disease course, MRI results, cerebrospinal fluid (CSF) findings, treatment, and relapse characteristics. Written informed consent was obtained from all patients. The study was approved by the ethics committee of The General Hospital of the People's Liberation Army, Beijing, China.

2.1. Clinical evaluation

Patient clinical characteristics included sex, age, season of rash onset, time duration of myelitis onset, interval between rash and myelitis onset, sides and segments of rash and myelitis, disease-related complications, medication history, personal and family history of autoimmune disease, treatment, VZV and myelitis relapse, neurological and systemic symptoms at the time of disease onset, and follow-up time. The Expanded Disability Status Scale (EDSS) (Hogan and Krigman, 1973) was used to analyze the severity of disease-related disability.

2.2. Laboratory findings

All patients underwent a full laboratory screening that included a complete blood cell count, renal and liver function, low-density lipoprotein cholesterol level, creatine kinase and protein levels, erythrocyte sedimentation rate, thyroid hormone levels, urinalysis, and tumor markers. Autoimmune serological evaluations included anti-nuclear and anti-extractable nuclear antigen antibodies, rheumatoid factor, complement levels, anti-neutrophil cytoplasmic antibodies, lupus anticoagulant, anti-β2-glycoprotein 1 and anti-cardiolipin antibodies, anti-aquaporin 4 (AQP-4) antibody, myelin oligodendrocyte glycoprotein (MOG) antibody, myelin basic protein (MBP) antibody, and thyroid autoantibodies. Two patients were also screened for ganglioside antibodies (GM1, GQ1b, GD1a, GT1B). In addition to varicella zoster virus, virological and bacteriological examinations included hepatitis C virus, hepatitis B virus, human immunodeficiency virus, Venereal Disease Research Laboratory (VDRL) test, and *Treponema pallidum* hemagglutination serological evaluations. All patients underwent CSF analysis.

2.3. Imaging

Magnetic resonance imaging of the cervical, thoracic, and lumbar sections of the spinal cord, including T1-weighted, T2-weighted, and gadolinium-enhanced T1-weighted imaging, was performed on all patients; At follow up, five patients underwent MRIs of the relevant section of the spinal cord. Brain MRIs were performed on all patients. Electromyogram was performed on four patients to assess potential injuries to the peripheral nerve.

3. Results

Our initial screening of patient records identified 15 cases that met our search criteria, of which five were excluded because of immune deficiency (1), optic neuritis without myelitis (2), or loss to follow-up (2). Medical histories for the remaining 10 patients included