Annals of Clinical Case Reports

Case Report
Published: 24 Jan, 2022

An Adult Varicella Case with Neuromyelitis Optica Spectrum Disorder: VZV Infection as Aggravating Rather than Initiator Factor

Yue Zhang[1], Xiaowei Zheng[1], Ling Ning[1], Wenyuan Li[1], Jing Yang[2], Beibei Huang[1], Hua Han[1], Yuanyuan Xu[1], Lei Wen[3], Yan Jiang[2], and Lei Li[1]*

[1]Department of Infectious Disease, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, China

[2]Department of Neurology, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, China

[3]Department of Ophthalmology, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, China

Abstract

Neuromyelitis Optica Spectrum Disorder (NMOSD) is a group of severe inflammatory demyelinating diseases of the central nervous system that affects the optic nerve and spinal cord. The pathogenesis of NMOSD is complicated, while therapies for NMOSD are limited and only partially effective in most cases. Virus infection is considered to be one of the causes of NMOSD. Presented is a patient with NMOSD and varicella. The diagnosis is confirmed by related auxiliary examinations, such as Varicella-Zoster Virus (VZV) antibody test and AQP4-IgG. In terms of treatment, on the basis of conventional antiviral treatment, high-dose glucocorticoid was given timely with the assistance of relevant departments, and the prognosis of patients has improved. Early, accurate diagnosis of patients with NMOSD that are critical to mitigate the risk of disability associated with this disease. Awareness of the potentially varied presentation of VZV myelitis can enable earlier recognition and specific treatment. Besides acting as initiator, VZV infection also can be an aggravating factor for NMOSD.

Keywords: Varicella; Varicella-zoster virus; Neuromyelitis optica spectrum disorder; Area postrema syndrome; Complications; Prognosis

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Correspondence:
Lei Li, Department of Infectious Disease, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, NO. 118 Fanhua Avenue, Baohe District, Hefei, 230051, China, Tel: 8618900518525; E-mail: lilei0403@163.com

Received Date: *20 Dec 2021*
Accepted Date: *20 Jan 2022*
Published Date: *24 Jan 2022*

Citation:
Zhang Y, Zheng X, Ning L, Li W, Yang J, Huang B et al. An Adult Varicella Case with Neuromyelitis Optica Spectrum Disorder: VZV Infection as Aggravating Rather than Initiator Factor. Ann Clin Case Rep. 2022; 7: 2102.

ISSN: 2474-1655

Abbreviations

NMOSD: Neuromyelitis Optica Spectrum Disorder; NMO: Neuromyelitis Optica; VZV: Varicella-Zoster Virus; ON: Optic Neuritis; RAPD: Relative Afferent Pupil Defect; MRI: Magnetic Resonance Imaging; DWI: Diffusion-Weighted Imaging; ADC: Apparent Diffusion Coefficient; OCT: Optical Coherent Tomography; CBC: Complete Blood Count; INH: Intractable Nausea or vomiting and Hiccups

Introduction

Varicella is a common self-limiting disease for children, while it may be more severe and complicated for some adult. Its primary infection causes chickenpox and can establish a lifelong latency in cranial nerves and the dorsal root ganglia [1]. If reactivated, it can cause herpes zoster. However, other serious complications are well recognized, including pneumonia, ataxia and encephalitis [2]. Neuromyelitis Optica Spectrum Disorder (NMOSD) is a group of immune-mediated central nervous system inflammatory demyelinating diseases, and the cause of NMOSD is still unclear [3]. Studies have shown that NMOSD is related to immune response initiated by viral infection [4].

Case Presentation

A 29-year-old woman was admitted to hospital with "fever with rash for 8 days, headache and blurred vision for 3 days" as the chief complaint on September 18th, 2020. Red papules appeared on the back and chest 8 days before admission (Figure 1, right panel). She was diagnosed with varicella 4 days ago and was given acyclovir treatment. Severe headache and blurred vision in the left eye suddenly occurred 3 days after the eruption of rash. After admission, relevant examinations were supplemented, and the acyclovir therapy was continued. Suddenly complained of pain and blindness of the left eye at September 19th afternoon, the visual field of the left eye was mostly

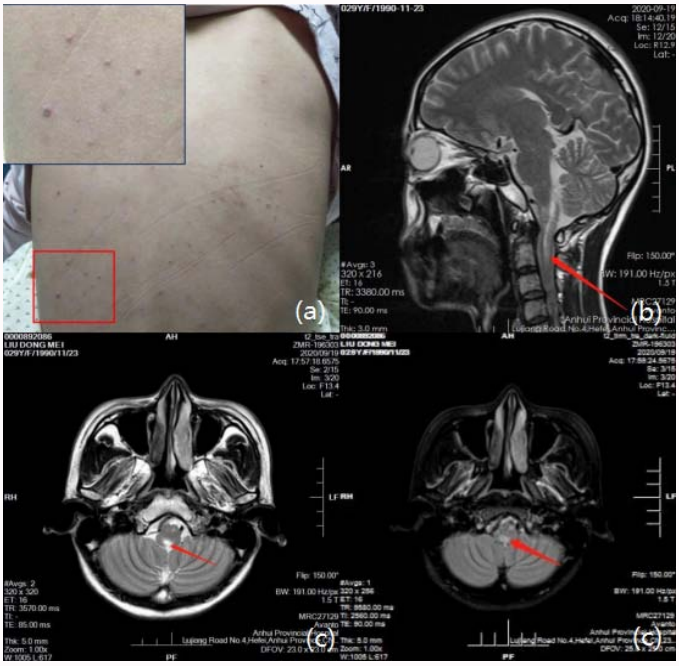

Figure 1: Clinical findings: (a) (Sep18th, 2020) Red papules appeared on the back and chest 8 days before admission. (b) (Sep19th, 2020) Sagittal T2-weighted head and cervical spine MR imaging showing hyperintense lesions longitudinally extended to C3, involving the central spinal cord, with bright spotty lesions. (c) (Sep19th, 2020) Axial T2-weighted Fluid-Attenuated Inversion Recovery (FLAIR) with hyperintense lesion in the brainstem involving the dorsal medulla (area postrema).

defective with right eye corrected visual acuity 1.0. Left conjunctiva was not hyperemia. Direct light reflection was weakened, but indirect is normal. Relative Afferent Pupil Defect (RAPD) (+), and the lens is transparent. The fundus optic papilla was edema and the boundary was unclear, but the patient re-examined the optic papilla after 3 months without edema and the boundary was clear. Two doses of dexamethasone were intravitreal injected. Serum VZV-IgG was detected. Brain Magnetic Resonance Imaging (MRI) prompts abnormal signal of medulla oblongata-cervical 3 spinal cord, left optic nerve thickened with peripheral effusion. The spinal cord of the medulla oblongata-cervical 3 is slightly swollen, and there are strips of long T1 and long T2 signals. The Diffusion-Weighted Imaging (DWI) shows a low signal, and the Apparent Diffusion Coefficient (ADC) shows a high signal, with an unclear boundary (Figure 1, right panel). Demyelinating antibodies detection showed AQP4-IgG was positive with a tilter of 1:32. Optical Coherent Tomography (OCT) of binocular optic papilla: The thickness of optic papillary nerve fibers in the left eye is significantly thicker than that in the right eye. The visual evoked electricity of the left eye is not elicited. Fundus photographic examination: The left optic papilla was edema; the boundary was unclear. To exclude other possible causes of NMO, the patient was examined for Complete Blood Count (CBC), erythrocyte sedimentation rate, C-reactive protein, serum biomarkers for HBV-HCV and HIV, but the results were all negative. Serum IgG were positive of rubella virus and cytomegalovirus, corresponding IgM negative. Varicella complicated with NMOSD was confirmed. Methylprednisolone (500 mg/day) combined with gamma globulin (20 g/day) and acyclovir (750 mg/day) was given. Visual field defect ameliorated gradually and returned to a state of blurred vision. After 5-day's treatment, oral prednisolone acetate, 50 mg/day, Mycophenolate mofetil 0.25 g twice a day were continued. Later, the left blurred vision significantly improved. Second MRI revealed abnormal signals of the spinal cord at the level of the medulla oblongata-cervical 2 vertebrae as well as cervical spine degeneration ameliorated. No neurological sequela was observed 3 months later. Left eye vision recovered slightly without pain. The corrected visual acuity of the right eye was 0.9, with left eye 0.2. The left conjunctiva and cornea, the direct and indirect light reflections were all normal RAPD (-). The lens was transparent with normal the optic nipple boundary and macular reflections. Binocular optic papilla OCT: The optic nerve thickness (90 micrometers) of the optic nerve of the left eye becomes thinner than that of the right (107 micrometers). VEP: P100 wave has a longer latency and lower amplitude in the left eye than the right. Fundus photographic examination revealed no abnormalities. So far, one year has passed, and the patient's prognosis has not improved significantly. There is no further improvement in vision, and occasionally symptoms of skin itching and local numbness of the limbs appear.

Discussion

Herpes Zoster Ophthalmicus (HZO) is defined as the reactivation of VZV inside the ophthalmic branch of the trigeminal nerve [5,6], commonly manifesting as conjunctivitis, anterior uveitis, or keratitis and rarely presenting with optic neuritis [7]. Neuromyelitis Optica (NMO) is a demyelinating disease with AQP4-IgG as specific antibody, which was included in the 2006 NMO diagnostic criteria. The concept of NMO was expanded to add Long Segments Transverse Myelitis (LETM), recurrent Optic Neuritis (ON), ON or LETM with autoimmune disease or autoimmune antibody positive are collectively referred to as NMOSD [3]. NMOSD patients mainly suffered from decreased vision [8]. Manifestations are diverse according to the location of intracranial, spinal cord lesions and the number of lesions [9]. Its characteristics are rapid onset, severe symptoms, rapid progress, and poor clinical prognosis. Therefore, early diagnosis and effective treatment are the keys to improve prognosis. Glucocorticoid is

indispensable for NMOSD treatment, although it may worsen chickenpox. According to the initial discussions of this case, it was considered that NMOSD was caused by VZV infection for the patient. For it has been accepted viral infection is a trigger for NMOSD [10]. The most common virus infections before NMOSD are VZV and so on [11]. It's in line with our conventional ideal. Studies show that average interval from skin rash to myelitis is 17.9 days (3~50 days) [12]. But its only 5 days in this patient. It's inconsistent with most existing reports of NMOSD after varicella. Therefore, we reviewed the patient's entire disease course and ask for more details. We noticed a detail ignored before: She developed intractable hiccups and repeated nausea and vomiting one month before admission. Gastroscope showed gastric retention and chronic gastritis and without improvement after treatment, which implies that hiccups are more likely to be caused by central causes. Thus, this patient may have already suffered NMOSD with area postrema syndrome as manifestation firstly before VZV infection, even though AQP4- IgG was unavailable then. Area postrema syndrome manifests as Intractable Nausea or vomiting and Hiccups (INH), which are often ignored. Patients often visited to gastroenterologist repeatedly for hiccups and vomiting [13]. In summary, the patient developed NMOSD with area postrema syndrome as the first symptom, and then suffered chickenpox. Five days post chickenpox, the symptoms of ON appeared and rapidly worsened. So VZV infection is an aggravating factor for NMOSD in this case. The article, A report of NMOSD Triggered by VZV Infection, reported by Turco [14] in 2020, shows that a patient had incoercible vomiting before the first appearance of herpes zoster, which is similar to the case, while there are differences between the conclusion of Turco's report and discussed case after objective analysis. A brand new idea maybe get, that is when VZV infection and NMOSD appear simultaneously, virus infection may be an aggravating, but not inducing factor. A complete medical history is asked in detail and completed AQP4-IgG, head MRI and other examinations are very important for early diagnosis of NMOSD.

Conclusion

Besides VZV infection is initiator for NMOSD as known before, maybe it also can act as an aggravating factor, especially when the NMOSD incubation period is shorter than usual.

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