# VZV low glucose case report

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Title Page

Varicella-zoster virus meningitis with hypoglycorrhachia: case report and literature review

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Varicella-zoster virus meningitis with hypoglycorrhachia: case report and literature review

Abstract

Background: Varicella-zoster virus (VZV) is a common viral infection, but meningitis is a rare complication of VZV infection. The cerebrospinal fluid glucose of viral meningitis is always within the normal range, which is different from bacteria, fungi, and cancerous meningitis. This paper reports a case of VZV meningitis with hypoglycorrhachia and the relevant literature was reviewed.

Case presentation: We report a case of an immunocompetent 39-year-old male, presenting with severe headache and fevers, without meningeal signs or exanthem, found to have VZV meningitis by the metagenomic next-generation sequencing of cerebrospinal fluid. The cerebrospinal fluid analysis revealed hypoglycorrhachia (cerebrospinal fluid glucose of 2.16) and he was treated successfully with intravenous acyclovir. Our literature review identified only ten cases diagnosed with VZV meningitis with hypoglycorrhachia previously reported to date in the English literature whose cerebrospinal fluid glucose was from 1.6 to 2.7mmol/L, with a ratio of cerebrospinal fluid to serum glucose from 0.30 to 0.49.

Conclusions: Although rare, the cerebrospinal fluid of patients with VZV meningitis may have hypoglycorrhachia, which broadens the understanding of the disease.

Keywords: hypoglycorrhachia, VZV, meningitis

## Background

Human herpesvirus type 3, also known as varicella-zoster virus (VZV), belongs to the herpesvirus family and is a human neurotropic virus, which can cause

two clinical manifestations including varicella and herpes zoster [1]. The initial infection, varicella, usually occurs in childhood, with fever and herpes as the main manifestations. VZV can be latent in the trigeminal ganglion and dorsal root ganglion for a long time and reactivate to cause herpes zoster, characterized by pain and rash distributed along the cutaneous ganglion [2]. Central nervous system involvement may occur at the time of initial infection or reactivation, which can be manifested as meningitis, encephalitis, meningoencephalitis, cerebrovascular disease, myelitis, Guillain Barre syndrome, and optic nerve retinitis, with or without skin rash [1,3].

Routine and biochemical examination of the cerebrospinal fluid plays an important role in identifying the cause of central nervous system infections and is important for initial empirical anti-infection treatment [4]. It is generally believed that the cerebrospinal fluid glucose of viral meningitis is normal (no less than half of the blood glucose in the same period), which is different from bacteria, fungi, and cancerous meningitis [5]. This paper reports a case of VZV meningitis with hypoglycemic changes in cerebrospinal fluid and the relevant literature was reviewed. A literature search with relevant keywords (including VZV and meningitis, or hypoglycorrhachia) was conducted in the PubMed databases up to December 2022.

Case presentation

The patient, a male, 39 years old, was admitted to our neurology department on November 19, 2020, because of a headache with nausea and vomiting, and a fever for six days. The patient had a mild persistent distending headache on November 13 without any inducement, accompanied by nausea and fatigue. And the headache worsened in one day with a visual analog scale of 9 points (0-10 points), accompanied by non-projectile vomiting once. He also had a fever,

with a body temperature of 37.5-38℃, and was out of spirit. He had no chills, cough, expectoration, dysuria, urinary frequency, or urgency.

On November 14, he went to a fever clinic. The complete blood count showed that white blood cell 9.59*109/L (normal range: 3.5-9.5*109/L), neutrophil cell 7.67*109/L (normal range: 1.8-6.3*109/L), and normal C-reactive protein. The screening test for influenza A and B, and COVID-19 were all negative. The head CT showed no obvious abnormality. After two days of analgesic and antipyretic treatments, the patient's symptoms did not improve. On November 16, he went to our emergency department. The second complete blood count was normal. Chest CT showed no signs of acute pneumonia. He was diagnosed with suspected meningitis. Since the patient refused to undergo lumbar puncture at the beginning, he was given acyclovir (500mg Q8h), ceftriaxone (2.0g QD), and mannitol empirically. The patient's headache was significantly relieved. However, he still had intermittent fever, with a temperature of up to 39℃. For further assessment and treatment, he was admitted to our neurology department. He had no new rash, no convulsions, no confusion, no mental behavior abnormalities, and speech and limb dysfunction these days. He had a history of epilepsy 25 years ago. He took carbamazepine and levetiracetam regularly, and his epilepsy had not relapsed in the past six years. He had an episode of varicella infection in his childhood, but no history of zoster since then. The rest of his medical history was unremarkable.

On physical examination on admission, the patient was afebrile and had no rash or abnormal neurological signs. Particularly, a stiff neck as a typical sign of meningitis was not found.

After admission, the complete blood count, serum electrolytes, blood urea nitrogen, creatinine concentrations, liver function, and erythrocyte sedimentation rate were all normal. Total serum protein was 60.2 g/L (normal

range: 65-85 g/L), and serum albumin was 36.5 g/L (normal range: 40-55 g/L). Except for a slight increase of D-dimer (0.38 mg/L, normal range<0.24 mg/L), other coagulation functions were normal. IgA, M, C3, and C4 were within the normal range. IgG was 6.32g/L (normal range: 7.23-18.85g/L). The flow cytometry test for T and B lymphocyte subsets was within the normal range. HIV, syphilis, hepatitis C and B virus screening were negative. The procalcitonin, (1,3)-beta-D-glucan, galactomannan test, cryptococcal antigen, and T-SPOT.TB was all negative. No obvious abnormalities were found in the electroencephalogram or enhanced magnetic resonance imaging of the brain. The patient underwent lumbar puncture examinations on November 19 and 30, with intracranial pressure of 240mmH2O and 140mmH2O respectively. Low glucose concentration, elevated protein concentration, and leukocyte counts were found (Table 1). No bacteria, cryptococcus, or acid-fast bacilli was found in the cerebrospinal fluid Gram, India ink, and acid-fast stain. There was a negative in cerebrospinal fluid culture. Cytology of the cerebrospinal fluid showed that there were many small lymphocytes, monocytes, a few ependymal-like cells, and neutrophils. On November 21, the metagenomic next-generation sequencing of the cerebrospinal fluid showed positive for human herpesvirus type 3, with sequence number 7, and the identification confidence of 99.0%.

The patient was finally diagnosed with VZV meningitis and continued intravenous acyclovir. And the ceftriaxone was stopped. On day 2 of hospitalization, the patient was afebrile. On December 1, he was discharged from the hospital and his symptoms were completely relieved. He refused a further lumbar puncture to recheck cerebrospinal fluid.

Discussion and conclusion

Aseptic meningitis is defined as clinical meningitis with negative bacterial cultures. The most common cause is enterovirus infection. VZV is a less common but important cause of aseptic meningitis, which can be seen in 8% to 13% of cases [6]. The DNA sequence of VZV detected by the polymerase chain reaction or next-generation sequencing, as well as the positive anti-VZV antibody IgM in cerebrospinal fluid and serum in the acute stage can help to diagnose the disease [3]. This patient, an adult male, has no definite immune deficiency, characterized by acute meningitis manifested as fever and headache. The number of leukocytes in the cerebrospinal fluid increases, mainly mononuclear cells. The next-generation sequencing of the cerebrospinal fluid found the specific DNA sequences of the VZV. Antiviral treatment was effective. It is considered that the diagnosis of VZV meningitis is definite.

The recent cutaneous herpes zoster may indicate the diagnosis of VZV meningitis. However, the typical VZV rash is absent in 33% to 60% of patients, creating a diagnostic challenge [7]. Our patient had no recent skin herpes zoster, and it is difficult to diagnose VZV meningitis only relying on clinical manifestation. In addition, cerebrospinal fluid examination of viral meningitis often shows an increase in leukocyte count, mainly lymphocytes, a slight increase in protein level, and normal glucose level [4]. The patient's cerebrospinal fluid glucose level was low, and the protein level increased significantly, which was atypical. Therefore, it is difficult to judge the pathogenic type of the patient in clinical practice. Next-generation sequencing of the cerebrospinal fluid has the advantages of being broad-spectrum and unbiased, which can achieve a rapid and accurate diagnosis. Practice shows that it has important application value in the diagnosis of meningitis [8]. This patient was finally diagnosed through this test.

The decrease of cerebrospinal fluid glucose level, namely hypoglycorrhachia, is defined as when the cerebrospinal fluid glucose is less than or equal to 45mg/dL or 2.5mmol/L. In addition, the normal ratio of cerebrospinal fluid to serum glucose is about 0.6, and lower than 0.5 is abnormal [9]. Low glucose changes in cerebrospinal fluid are common in bacteria, tuberculosis, and fungal meningitis. The rare causes include acute syphilitic meningitis, mycoplasma pneumonia meningitis, primary amoebic meningitis, meningococcal cysticercosis, malignant meningitis, subarachnoid hemorrhage, sarcoidosis, rheumatoid meningitis and lupus myelopathy [10]. In addition, some viral meningitis cerebrospinal fluid may also have low glucose changes, including lymphocytic choroid plexus meningitis virus, mumps virus, Echovirus, coxsackie virus, herpes simplex virus, and VZV reported in this paper [11]. Very few cases of VZV meningitis with low cerebrospinal fluid glucose were reported. After the literature review, we found only ten patients with VZV meningitis had hypoglycorrhachia previously reported to date in the English literature (Table 1) [7, 11-17]. These ten immunocompetent patients are 12 to 44 years old, with headache as the main manifestation, with or without fever, and most of them did not have the rash. The cerebrospinal fluid glucose is 1.6-2.7mmol/L, with a ratio of cerebrospinal fluid to serum glucose 0.30-0.49, and elevated cerebrospinal fluid protein (86-264 mg/dl) and leukocyte (20-1720 cells/mm3). After anti-viral treatment, all these patients had benign prognoses. According to the improvement of the patient's clinical manifestations, antiviral treatment was considered to be effective, which is consistent with the diagnosis of VZV meningitis. After treatment, the patient had a lower glucose level in cerebrospinal fluid in the second lumbar puncture, considering the delayed recovery of glucose in cerebrospinal fluid after treatment as reported before [12]. Unfortunately, the patient did not recheck the cerebrospinal fluid to

confirm whether the glucose level returned to normal with the recovery of meningitis. Otherwise, the patient has a history of epilepsy and changes in low glucose in cerebrospinal fluid. Attention should be paid to the identification of glucose transporter 1 deficiency syndrome, but the disease generally has the characteristics of psychomotor development backwardness, paroxysmal dyskinesia, and cerebrospinal fluid sugar is usually lower than 2.2 mmol/L. This patient is inconsistent with this [18].

In conclusion, we report a case of adult VZV meningitis confirmed by next-generation sequencing of cerebrospinal fluid samples. The cerebrospinal fluid of patients with VZV meningitis may have hypoglycorrhachia, which broadens the understanding of the disease.

List of abbreviations

VZV: varicella-zoster virus

Declarations:

Ethics approval and consent to participate

Informed consent was obtained from the patient to publish this case, and approval for this study was provided by the Research Ethics Committee of The First Hospital of Peking University.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Availability of data and materials

All data related to this case report are documented within this manuscript.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

LJC and YMZ contributed to the drafting, and reporting of the case. FL and HJH contributed to the revision of the manuscript. FG contributed to the concept and revision of the manuscript. The authors read and approved the final manuscript. All authors met the authorship criteria from the International Committee of Medical Journal Editors (ICMJE).

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