Varicella-zoster virus-associated meningitis followed peripheral facial palsy: A case report

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Abstract. Although central nervous system infection following varicella zoster virus infection is relatively common, subsequent peripheral nervous system infection is comparatively rare. The present case documents a case of meningitis after varicella-zoster virus (VZV) infection, which was then followed by peripheral facial palsy. Specifically, a 54-year-old female patient was first admitted to Shengli Oilfield Central Hospital (Dongying, China) with headache and fever. Physical examination revealed herpes that formed along the intercostal nerve in the left forebreast, armpit and back. Subsequently, neurological examination found cervical resistance in more than three fingers (neck resistance of less than two transverse fingers is not evidence of meningeal irritation; the neck resistance of this patient was approximately three transverse fingers, so the patient was presumed to be positive for meningeal irritation, highly suggestive of meningitis) and Kernig sign was positive. There were no significant abnormalities according to brain MRI and lumbar puncture pressure was 330 mmH_2O. In addition, the leukocyte count was 734x10^6/l, 50% monocyte count, 50% multinucleated cells, chloride levels of 109.1 mmol/l, protein levels of 235 mg/dl and glucose levels of 4.18 mmol/l in the cerebrospinal fluid. DNA and RNA metagenomic detection of pathogenic microorganisms in the cerebrospinal fluid revealed the presence of VZV. The patient was therefore treated with acyclovir, ceftriaxone, mannitol and methylprednisolone, but then developed right peripheral facial palsy at 10 days after treatment. This complication was not found in the literature, and the occurrence of facial neuritis was unexpected. The active period of VZV virus was 21 days, and the patient had herpes 5 days before admission. The active period of the virus was considered to have subsided and the patient was in the recovery period. Moreover, the results of lumbar puncture showed that the white blood cells, the proportion of neutrophils and the protein in cerebrospinal fluid were all decreasing, which also indicated that the patient had entered the recovery period. The patient was discharged 18 days after admission. In conclusion, observations from the present case suggested that the clinical manifestations of VZV infection can be complex and varied, requiring the clinician to have an accurate understanding of its disease progression and treatment.

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Introduction

Herpes zoster (HZ) is an infectious virus that mainly affects the nerves and skin. It is caused by the varicella-zoster virus (VZV) and typically manifests itself as shingles in adults because the rash appears in blisters and is distributed in bands (1). The VZV genome is a linear double-stranded DNA molecule of ~125,000 bp that encodes at least 71 unique open reading frames (ORFs) and related promoter sequences. VZV particles are 80-120 nm in diameter (2). Linear VZV genomes are packaged into an icosahedral nucleocapsid core that is formed from proteins encoded by ORF20, ORF21, ORF23, ORF33, ORF40 and ORF41. Capsids are surrounded by a tegument layer, which is a less well-defined structure that is made up of proteins with known or predicted regulatory functions, including the immediate-early (IE) viral transactivating factors that are encoded by ORF4, ORF62 and ORF63, those that are encoded by the ORF9-ORF12 gene cluster, and viral kinases ORF47, ORF66, ORF8, ORF48, ORF59 and ORF13 (3).

The outer virion component is a lipid membrane envelope that is derived from cellular membranes with incorporated viral glycoproteins, including gB/gH-gL, which forms the minimal fusion complex. VZV gC and gE have been implicated in membrane attachment, whereas gB, gH, and gL are the necessary components for cell entry where the virion must deliver the capsid through the plasma membrane to initiate infection. The most well-characterized glycoproteins are those that function in membrane fusion, gB, gH, and gL (4). In common with all herpesviruses, after VZV binds to cell surface proteins, the gH-gL heterodimer is thought to prime gB to enable a gross conformational change from a prefusion

to postfusion structure, leading to fusion of the virion envelope with the plasma membrane (5).

By contrast, VZV mainly appears as chickenpox in children following infection, who have no immunity to the virus. A portion of patients will exhibit no symptoms following infection but will instead harbor the virus (6). It can remain latent in the dorsal root ganglion of the spinal cord for long periods of time following infection due to its neurotropism (7), where it can 'reactivate' and reproduce again when the immune system becomes compromised or because of diminished cell-mediated immunity to the virus in such individuals (8). When this occurs, it moves along the nerve fibers to the skin surface, where they trigger a potent inflammatory reaction, which usually appears as a painful or pruritic cutaneous vesicular eruption that occurs in a characteristic dermatomal distribution (9). This rash is generally unilaterally and segmentally distributed and consists of clusters of herpes, and the patient will start to feel pain (neuralgia). It is mostly distributed along the intercostal nerve, and occurs more naturally in the chest, and there is no difference between the left and right sides. The older the patient, the worse the neuralgia tend to be (10,11). The diagnosis of the disease is based on the association with neurological symptoms and signs after the onset of the rash, as well as the presence of VZV virus in the cerebrospinal fluid as demonstrated by PCR, a 4-fold increase in the titer of anti-VZV IgG in peripheral blood indicating persistent viral infection and positive anti-VZV IgM indicating recent infection/reactivation (12). Reactivation of VZV may also cause a wide variety of neurological syndromes, which is treated with corticosteroids and the antiviral drug acyclovir (13).

VZV infection is particularly common during the spring and autumn because the air temperature difference is large, the level of human immunity is low and individuals tend to spend more time outside in public. The incidence of infected adults tends to be higher compared with that of children; the global incidence rate of HZ ranges from 3 to 5/1,000 person-years and from 5.23 to 10.9/1,000 person-years in individuals ≥50 years of age (14,15). In addition, this incidence increases significantly with age. It has been found in a prospective study of viral infections in the CNS in Spain that VZV was considered to be the second most common cause of infection in adults with meningitis and encephalitis in 2013 (16,17). Both the central nervous system and peripheral nervous system can be involved following VZV infection (18,19), However, these two articles only describe meningitis and myelitis caused by VZV infection, and, to the best of our knowledge, the present study is the first case reported where the changes of facial neuritis secondary to meningitis were found.

Case report

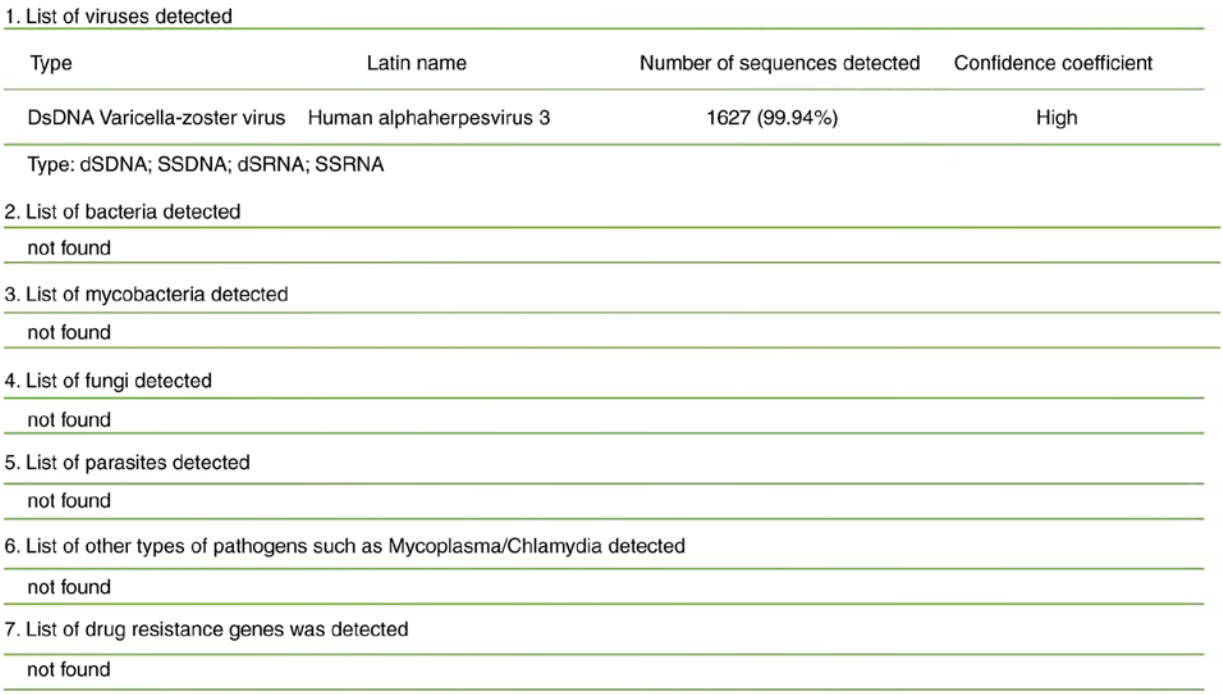
A 59-year-old female patient first presented to Shengli Oilfield Central Hospital (Dongying, China) with a headache for 2 days before admission (July 2023). This patient could not accurately describe the location of this headache, which was accompanied by nausea and vomiting. There was no eject-like vomiting (which would have suggested intracranial hypertension and possible meningitis or encephalitis), fearless of light and sound (the accompanying symptoms of migraine were photophobia and phonophobia, and the patient was admitted to the hospital for headache in order to differentiate it from migraine), no unconsciousness and confusion, no slurred speech and no numbness or weakness of limbs. However, the patient did suffer from a fever 1 day before admission, with a maximum temperature of 39˚C, accompanied by myalgia and diarrhea (with yellow soft stool). The patient was therefore hospitalized in Hekou Peoples' Hospital (Shandong, China; July 2023), where and her brain MRI showed no obvious abnormalities. The novel coronavirus disease-19 nucleic acid test returned negative. However, there was no improvement following anti-inflammatory rehydration treatment (normal saline 250 ml + 1.5 g cefuroxime sodium; 0.5 h; twice a day). Therefore, for further diagnosis and treatment, this patient was referred to Shengli Oilfield Central Hospital after 1 day of hospitalization in the local area. However, Shingles appeared on the left anterior chest, armpit and posterior back 5 days before admission to Shengli Oilfield Central Hospital. The patient denied any history of other medical conditions, but had an uncertain history of chickenpox during childhood and had no history of varicella vaccination. Physical examination revealed a body temperature of 39˚C, pulse 75 bpm, respiratory 18 bpm and blood pressure of 124/71 mmHg. The blisters along the intercostal nerve were broken and the skin was red and crusted. Shingles could still be observed on the skin surfaces of left anterior chest, armpit and posterior back, which had been ruptured. However, the skin surfaces had no blood or fluid seepage.

Nervous system physical examination revealed a clear consciousness but poor mental state (the patient could answer questions correctly and speak weakly). The patient exhibited clear speech and normal advanced intelligence (contains memory, calculation, understanding, judgement and directional forces). The eyes had large and round bilateral pupils (with diameters ~3 mm) and were sensitive to light response as normal, with negative nystagmus and adequate eye movement. There was also bilateral nasolabial groove symmetry, with the tongue extending centrally, bilateral soft palate mobility and centered uvula, where the pharyngeal reflex was normal. Limb muscle strength was found to be grade 5 with normal muscle tension, bilateral tendon reflex symmetry (++) and negative bilateral pathological signs. Finger-to-nose test and Heel-knee-tibia test could be completed accurately, bilateral pain and temperature perception were symmetrical; however, testing revealed neck resistance of 3 fingers width (when the patient is in a supine position and lifts their head, the distance between the jaw and sternum is measured. If this distance can accommodate less than two finger widths, it is considered unlikely for meningitis to be present) and positive Kernig sign.

Upon admission, blood routine examination and C-reactive protein (CRP) tests showed white blood cell counts of 11.7 (3.5-9.5)x10^9/l, neutrophil counts of 7.55 (1.8-6.3)x10^9/l, CRP levels of 46.40 (0-10) mg/l and Tetrad + D-D dimer: DD levels of 1.43 (0-0.5) mg/l. Biochemical tests revealed total protein levels of 60.4 (65-85) g/l, albumin levels of 35 (40-55) g/l, glucose concentrations of 9.55 (3.89-6.11) mmol/l, K^+ levels of 3.41 (3.5-5.3) mmol/l, Na^+ levels of 132.6 (137-147) mmol/l and Cl^- levels of 98.2 (99-110) mmol/l. Tumor marker testing found neuron-specific enolase levels to be 16.40 (0-16.3) ng/ml. No abnormalities were found for hepatitis B, hepatitis C, syphilis and HIV and the urine test revealed no abnormalities.

Table I. Changes of cerebrospinal fluid indexes after lumbar puncture.

CSF (cerebrospinal fluid)	White blood cell count (10^6/l)	Proportion of leukocyte monocyte count (%)	Proportion of multinucleated cells (%)	Protein levels (mg/dl)	Glucose levels (mmol/l)	Chloride concentrations (mmol/l)
1st lumbar puncture	734	50	50	253	4.18	109.1
2nd lumbar puncture	329	98	2	178.6	4.2	107.7
3rd lumbar puncture	156	99	1	144.7	3.68	114.3


1. List of viruses detected

Type	Latin name	Number of sequences detected	Confidence coefficient
DsDNA Varicella-zoster virus	Human alphaherpesvirus 3	1627 (99.94%)	High

Type: dSDNA; SSDNA; dSRNA; SSRNA

2. List of bacteria detected

not found

3. List of mycobacteria detected

not found

4. List of fungi detected

not found

5. List of parasites detected

not found

6. List of other types of pathogens such as Mycoplasma/Chlamydia detected

not found

7. List of drug resistance genes was detected

not found

Figure 1. DNA and RNA metagenomic detection of pathogenic microorganisms in the cerebrospinal fluid. Varicella zoster virus was detected (MolPure® Viral DNA/RNA Kit Viral DNA/RNA Extraction; cat. no. 19321ES50; Yisheng Biotech). Nucleic acid quality verification steps: i) The A260/A280 ratio of high-quality DNA should be between 1.7 and 1.9, and the A260/A230 ratio should be >2. The DNA quality can be verified by 1% agarose gel electrophoresis (no stray bands, no trailing, no protein contamination in the background). ii) DNA integrity test: If most of the fragments were below 200 nt (except plasma free DNA, 140 nt), the DNA degradation was serious and should be re-extracted. iii) The A260/A280 ratio of high quality RNA should be between 1.8 and 2.0, and the A260/A230 ratio should be >2. iv) The trace amount of nucleic acid was quantitatively determined by Qubit fluorescent dye method [Sequencing type: i) Sequencing direction: Single-end sequencing; ii) Sequencing length 50 bp. dsDNA HS Assay Kit for Qubit® (cat. no. 12640ES60/76; YiSheng Biotechnology); Loading concentration of the final library, >30.3 nmol; qubit 4.0 measurement method].

According to the blood test results, the patient had infection, protein and electrolyte deficiencies in the blood and hypercoagulable states, and the tumor marker neuron-specific enolase was slightly higher than the normal reference value, which had little clinical significance.

Lumbar puncture examinations were completed three times, once in July 2023 and twice in August 2023. No abnormalities could be found following cerebrospinal fluid (CSF) ink staining and acid-fast staining, where the routine CSF white blood cell count was 734 → 329 → 156x10^6/l. The proportion of leukocyte mononuclear cells in the CSF was 50 → 98 → 99% and the proportion of multinucleated cells in the CSF was 50 → 2 → 1%. CSF protein levels were found to be 253 → 178.6 → 144.7 mg/dl, glucose levels were 4.18 → 4.2 → 3.68 mmol/l and Cl^- levels of 109.1 → 107.7 → 114.3 mmol/l (Table I). DNA and RNA metagenomic sequencing detection of pathogenic microorganisms in the CSF (DNA + RNA) by No EU medical laboratory (Guangzhou, China) revealed VZV (Figs. 1 and 2).

According to imaging examinations, heart + lower limb venous ultrasound found mild tricuspid valve regurgitation and small quantities of pericardial effusion but no venous thrombosis of lower limb. Chest and abdominal CT (Siemens SOMATOM Force; Imaging parameters: layer thickness 5 mm, layer spacing 5 mm, voltage 120 KV, current 225 mA, matrix 512x512) found multiple small nodules in both lungs, where mild edema in bilateral pleural cavity was revealed (Fig. 3A and B). A hepatic cyst, cholecystitis and mesenteric panniculitis were also revealed (Figs. 4-6). The pancreas was a normal shape and size, with no discernible abnormalities in its parenchyma. The pancreatic duct did not display any signs of dilation; the spleen demonstrated a normal shape and size, without any abnormalities in its parenchyma; there was no significant expansion or fluid accumulation observed in

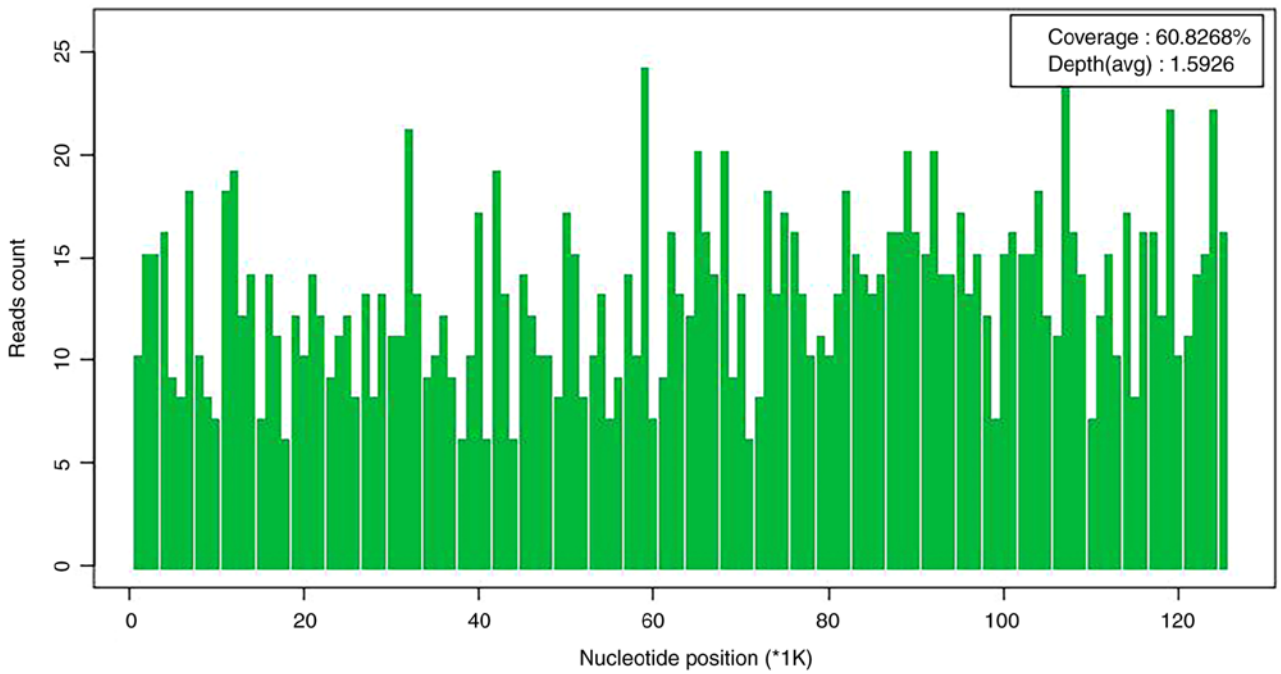


Figure 2. DNA and RNA metagenomic detection results. In the results of this detection, the total length covered by the genome sequence of this species was 76,084 bp, the coverage was 60.8268% and the average depth was 1.5926X.

Figure 3. Chest CT imaging results. Multiple small nodules were observed in both lungs, the largest nodule was 6 mm in diameter. Small quantities of fluid in bilateral pleural cavity was also seen. (A) The location of the arrow in the lung window is the nodule, (B) the position indicated by the arrow in the mediastinal window is pleural effusion. P, posteria; L, left; R, right.

the stomach and intestines, and there were no evident masses present; the kidneys and adrenal glands exhibited normal size and shape, with no abnormalities detected in their parenchyma; there were no abnormalities found in the renal pelvis or ureters on both sides.

Reexamination of the brain MRI (Siemens Trio Tim 3.0T; Scanning parameters: repetition time (TR)/echo time (TE) 5,860 ms/93 ms, repetition time (Ti) 2,003 ms, layer thickness 5 mm, layer spacing 1 mm, field of view 26x26 cm, matrix 256x256) in August 2023 showed no significant abnormality (Fig. 7A and B).

As a result, the patient was treated with the following regimen (13): i) Mannitol 125 ml intravenous (IV) drip q12 h (for 6 days) + 125 ml IV drip qday (Mannitol was tapered for an additional 2 days); ii) normal saline (NS) 100 ml + 2 g ceftriaxone (Rocephin) IV drip qday (for 7 days); iii) NS 250 ml + 0.5 g acyclovir IV drip q8 h [for 16 days, followed by sequential oral therapy (0.5 g q8 h) until day 21]; and iv) NS 100 ml + methylprednisolone sodium succinate 80 mg IV drip qday (for 5 days). The patient presented with fever and headache upon admission. Physical examination revealed neck stiffness of three fingers, positive Kernig's sign and herpes on the anterior chest and back in the distribution of intercostal nerves, consistent with HZ. Combined with the results of lumbar puncture at admission, these findings suggested the presence of VZV meningitis and intracranial hypertension in the patient. Therefore, the present study initiated treatment upon admission including mannitol for dehydration and reduction of intracranial pressure, ceftriaxone for antibiotic therapy, acyclovir for antiviral treatment and methylprednisolone for anti-inflammatory purposes. On the third day of treatment, the temperature of the patient returned to within normal range, and her mental status exhibited significant improvement compared to prior assessment, transitioning from a state of lethargy to

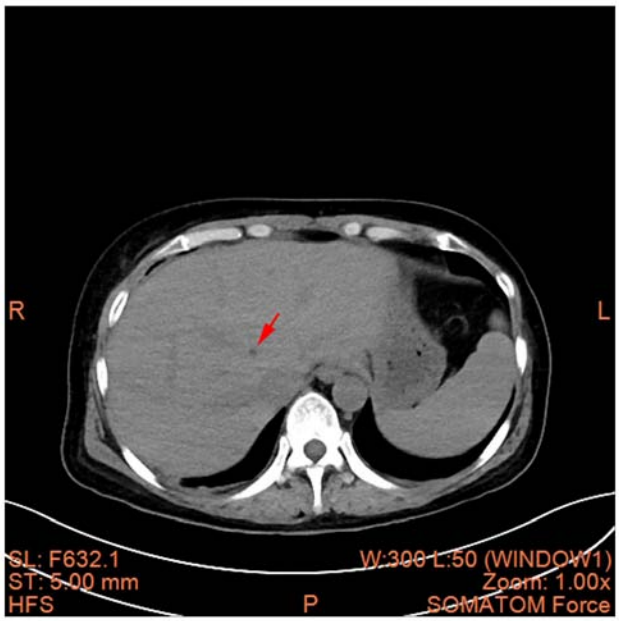


Figure 4. Hepatic cyst. The red arrow indicates that there was a cystic hypodense shadow of ~5 mm in diameter in the liver.

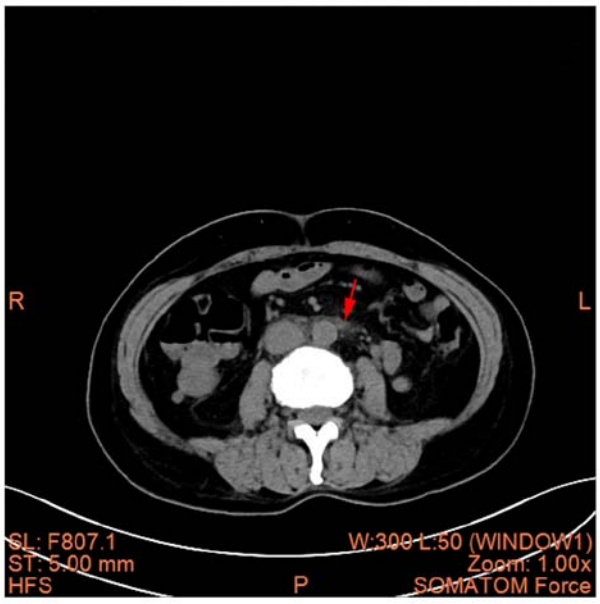


Figure 6. Mesenteric panniculitis. The red arrow indicates that the density of the mesenteric area was increased, and multiple small lymph nodes were seen.

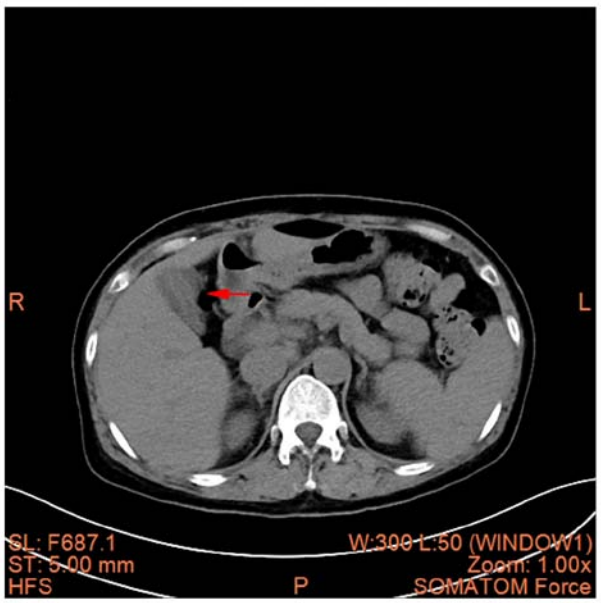


Figure 5. Cholecystitis. The red arrow indicates that the size and shape of the gallbladder were normal, the wall of the gallbladder was thickened, and effusion was observed in the gallbladder fossa.

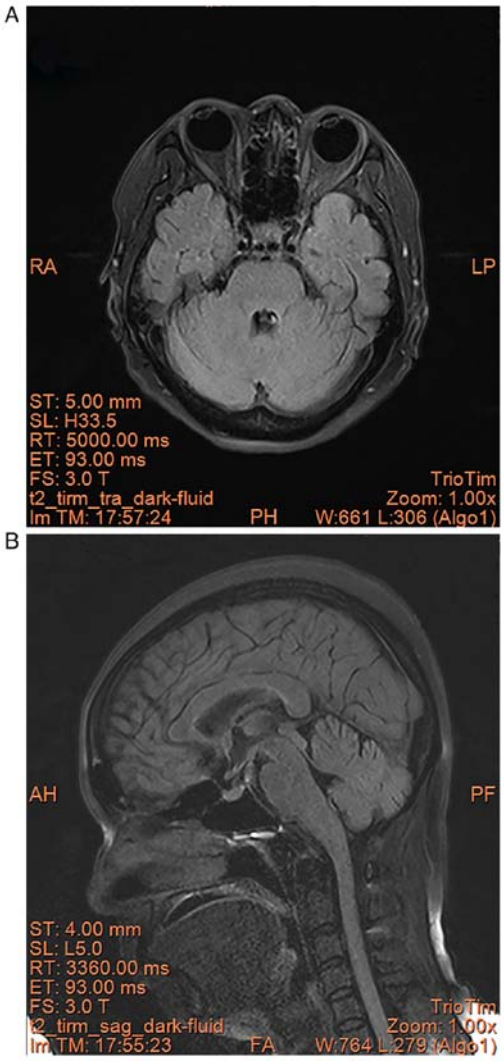


Figure 7. Brain MRI results. No significant abnormality could be seen (A) axial and (B) sagittal views. RA, right anterior; LP, left posterior; AF, anterior frontal; PH, posterior head.

heightened alertness. Consequently, methylprednisolone was discontinued on day 5 of treatment while ceftriaxone was ceased and mannitol dosage reduced after 1 week of therapy, taking into consideration the effective control of meningitis. Acyclovir monotherapy was continued (Fig. 8).

At 10 days after admission (August 2023), the patient developed right peripheral facial paralysis, but no significant abnormality was found in brain MRI. After reexamination, prednisone acetate 30 mg qday, mecobalamine 0.5 mg tid (20), vitamin B1 10 mg tid, potassium chloride tablet 0.5 g tid and calcium carbonate 300 mg qd (for 7 days) were treated orally (21). However, on the tenth day of hospitalization, the

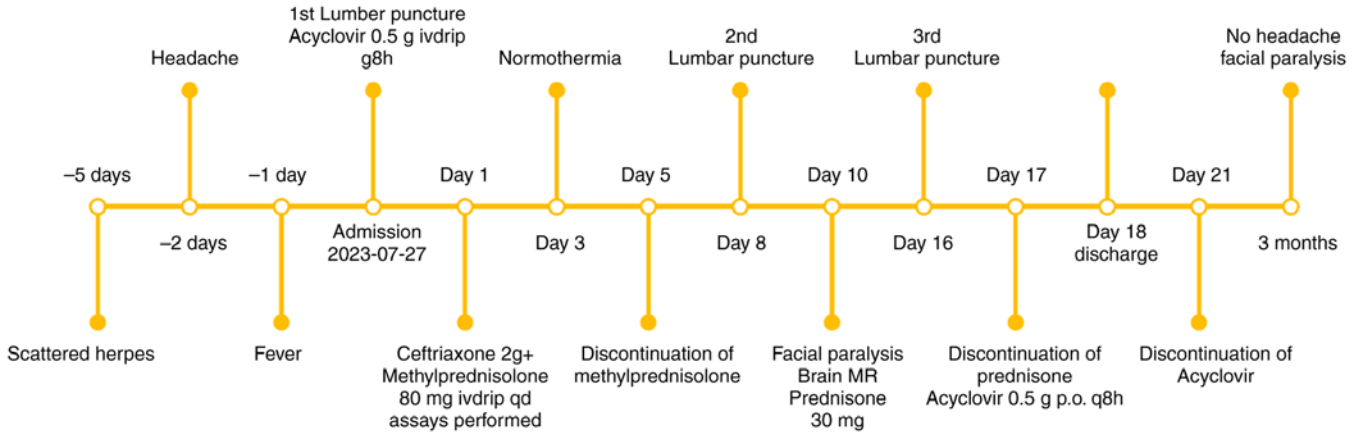


Figure 8. A flowchart of the patient's treatment.

patient presented with symptoms of facial paralysis, prompting resumption of oral prednisone for anti-inflammatory treatment. Additionally, methylcobalamin and vitamin B1 were administered for nerve nutrition therapy, potassium chloride was supplemented to mitigate hormone-induced electrolyte imbalance side effects and calcium carbonate was provided as a preventive measure against hormone-induced osteoporosis (Fig. 8).

Based on the findings of high fever, dizziness, neck resistance and positive Kernig's sign on physical examination which, combined with the results of lumbar puncture and CSF and meta-genomics sequencing results, meningitis was considered. After a 10-day treatment period, the patient exhibited several symptoms suggestive of right peripheral facial paralysis. The afferent nerve of the corneal reflex is the ophthalmic branch of the trigeminal nerve, the efferent nerve is the facial nerve, and the facial nerve innervates the orbicularis oculi muscle. If the facial nerve has inflammation, then its frontal branch, temporal branch, zygomatic branch, buccal branch, and mandibular branch will have dysfunction (22). These branches are all motor function nerves, patients will have frontal wrinkles that are shallower than the opposite side, their eyes will not close, the nasolabial groove will be shallower than the opposite side and they will be leaking air while puffing up cheeks (23). Specifically, in the present patient, the right frontal lines became shallow, the sclera of the right eye became visible when the eye was closed, the right nasolabial fold appeared shallow and there was leakage air on the right side of the cheek. Therefore, the patient was diagnosed with meningitis in addition to peripheral facial palsy caused by VZV reactivation.

On the 17th day of admission, the patient received a 1 week course of prednisone acetate for Bell's palsy; however, there was no significant improvement in facial paralysis symptoms at that time. The efficacy of prednisone acetate and B-vitamins in reducing post-paralysis sequelae could only be confirmed 2 weeks later. Considering the significant improvement in the third lumbar puncture results on the 17th day of admission, with notable reductions in cerebrospinal fluid white blood cells and protein levels indicating effective control of VZV virus infection, intravenous acyclovir antiviral treatment was sequentially followed by oral administration as the patient entered into the recovery phase. Consequently, the patient was discharged from the hospital on the 18th day of admission. Following discharge, the patient continued to receive oral acyclovir antiviral treatment until the 21st day (Fig. 8).

At 3 months after discharge (November 2023), a follow-up was be conducted (meningitis was considered on admission and was discharged after 21 days of treatment), the patient described that the headache was significantly relieved. The fever had subsided, but the sequelae of the right facial nerve paralysis persisted. The eyes were not tight (the sclera was visible when the eyes were closed) on the right side, air leaked from the right corner of the mouth when puffing out cheeks and the right corner of the mouth drooped when smiling. These were sequelae of facial neuritis, rehabilitation can be opted for improving the aesthetics of the face, but the chances of fully recovering are slim (24). The present study suggested further acupuncture treatment, but the patient and their family felt that the current symptoms of facial paralysis only affected appearance and not daily activities or life, so the patient was unwilling to continue with rehabilitation treatment. The recent follow-up results (March 2024) showed that there were no more symptoms of headache and fever, and compared to 3 months after discharge, there was no significant change in the symptoms of right facial paralysis.

Discussion

The probability of central nervous system injury after VZV infection is only between 0.1 and 0.3% in patients with healthy immune systems (25). However, to the best of our knowledge, facial neuritis secondary to meningitis after VZV infection has not been reported before. The present case documented a patient who contracted meningitis 5 days after VZV infection and unilateral facial neuritis 2 weeks later. At present, the pathogenesis of this condition remains unclear, both of which are presented in the present case. Namely, the nerve injury caused by meningeal inflammation after VZV infection and the potential secondary mechanism of nerve damage caused by immune-mediated inflammatory response, similar to the pathogenesis of Guillain-Barre syndrome (26). The pathogenesis of VZV-associated neuroinflammation involves a complex interplay between viral replication within sensory

ganglia and immune-mediated responses that contribute to tissue damage and dysfunction. Upon primary infection, VZV gains access to sensory ganglia, establishing latent infection within neurons. During reactivation, the virus can spread along sensory nerves, triggering a cascade of inflammatory mediators, chemokines, and immune cell infiltration in the affected neural tissues (27). This then promotes VZV penetration through the blood-brain barrier to reach the intracranial secondary meninges (28). Since the facial nerve can reach into the leptomeninges and extracranial regions, Ottaiano *et al* (29) describes in detail the process of the facial nerve exiting from the brainstem nucleus and passing through the dura mater; the inflammation may then spread to the cranial nerves through the meninges. Furthermore, the aberrant activation of the natural defense mechanism, characterized by the dysregulated production of immunomodulatory proteins and chemokines, has been implicated in the pathogenesis of VZV-induced neurological disorders, such as encephalitis, myelitis and vasculopathy (30). Liu *et al* (30) divided 28 patients with VZV infection complicated with meningitis into a good prognosis group and a poor prognosis group. After analysis, it was found that cerebrospinal fluid IL-18 may be an important reference index for the prognosis of patients. In the proteomic analysis of cerebrospinal fluid, proteins (CXCL10, ELANE, IL-1RN, MPO, PRTN3, WARS1, TYMP) related to inflammation and immune cell activation are upregulated, while proteins (CKMT1B, SLITRK3, Synaptotagmin-3, KIF5B) related to nerve function and energy metabolism are downregulated (31).

In the present case, the patient was given 80 mg/day of methylprednisolone for 5 days, which was stopped after the patient's body temperature returned to normal. However, facial neuritis occurred 5 days after the glucocorticoid was stopped, and 30 mg/day of prednisolone acetate was provided as oral treatment, which was sustained for 1 week. There have also been reports on the dosage and course of glucocorticoid used after VZV infection (32,33).

In a previous Japanese patient with Hunt syndrome secondary to polycranial neuritis and meningitis, the patient was given 1 g/day methylprednisolone shock treatment for 3 days and changed to 40 mg/day oral treatment with prednisolone acetate and then gradually reduced to 5 mg/day within 7 weeks. The patient was discharged from hospital upon recovery; however, the patient's weight was not taken into consideration during the administration of a cortisone shock treatment (34). The standard dosage for corticosteroid shock therapy is 1,000 mg. However, upon reviewing the patient's weight, which was ~70 kg, the given dosage was closer to 14.3 mg/kg (34). The use of high-dose corticosteroids can lead to secondary infections and osteoporosis with femoral head fractures. After careful consideration, the present patient had a body temperature of 39˚C when she was admitted to the hospital, but the ECG monitoring showed that the heart rate, blood pressure, respiration, and oxygen saturation were stable, and the laboratory indicators were not critical value. After careful consideration, the patient was given ~1.5 mg/kg methylprednisolone. The patient received the normal adult dose (35), without undergoing steroid pulse therapy like the Japanese patient who recovered and was discharged. However, in this case, the patient still had residual facial neuritis upon discharge. We hypothesize that this may be related to insufficient steroid dosage. For patients with VZV-induced meningitis, it might be advisable to initially opt for corticosteroid shock therapy. Additional attention to this treatment regimen under similar circumstances should be paid in the future.

The body temperature of the present patient fluctuated at 38-39˚C during the first 3 days where her consciousness began to be blurred (between drowsiness and lethargy, on the day of admission, the patient's consciousness went from being alert to drowsy, and on the second day of admission it progressed from drowsiness to lethargy. After treatment, on the third day of admission, it shifted from lethargy to clear consciousness). In combination with the color of the CSF, white blood cell count and neutrophil ratio, ceftriaxone 2 g/day anti-inflammatory treatment was given to the patient. The family members of the patient strongly requested for the replacement of ordinary ceftriaxone with Rocephin treatment after 1 day of anti-inflammatory medication. Patient consciousness gradually improved and the peak temperature gradually returned to normal, rendering stoppage of the anti-inflammatory treatment after 1 week. Administration of ceftriaxone (Rocephin) for VZV-associated meningitis has been previously reported. Shahkarami *et al* previously reported a young male patient with VZV infection complicated with intracranial streptococcal infection, who was given ceftriaxone 2 g (IV drip; bid) for 2 weeks and was discharged from hospital after a complete recovery (36). Therefore, the use of ceftriaxone should be individualized according to the patient's situation. At the beginning of the treatment, this patient was administered domestically produced ceftriaxone and indeed experienced persistent high fever, gradually progressing to a state of drowsiness and eventually lethargy. The present study promptly switched to imported Rocephin for treatment, resulting in a reduction in peak body temperature and improvement in consciousness. Considering the reported case by Shahkrarami, we will consider administering Rocephin directly for future cases of VZV-induced meningitis.

A majority of children suffering from stroke have been documented for this to be attributed to VZV infection (37). VZV enters the brain through the reactivation of the latent virus in the trigeminal ganglion and by transaxonal migration to infect the cerebral arteries. In the pediatric population, VZV mostly affects the larger arteries, and in the adult population, it affects both medium- and large-sized arteries, with increased risk among immunocompromised (37,38). VZV infection can cause cerebral artery lesions, promoting the risk of stroke (37). Therefore, in clinical practice, it is necessary to screen for the causes of stroke in children with VZV infection, where lumbar puncture examination should be improved (39). Although the present patient was not a child with stroke, her experience was similar to numerous cases of teenagers who have had strokes after upper respiratory tract infections, and we considered that lumbar puncture was needed to rule out viral infection in this uncommon population of patients with cerebral infarction.

After admission, the fasting blood glucose levels of the present patient was 9.55 mmol/l and no increase in fasting blood glucose or 2 h after three meals were observed in the follow-up surveillance about the finger blood glucose, which was considered to be associated with the application of glucocorticoids in the course of treatment. However, previous studies

have found that the increase in blood glucose can increase the risk of VZV infection by 20%, the risk of HZ increases in the diabetes group compared with the non-diabetes group (RR 1.2; 95% credibility interval, 1.17-1.22) (40,41). Due to the low innate immune response of polymorphonuclear cells and mononuclear/macrophages in patients with diabetes (42), it is necessary to improve the screening for diabetes for such patients. It has been previously reported that VZV infection was associated with 'invisible' diabetes (abnormal glucose tolerance or impaired fasting blood glucose regulation) (43). The susceptibility to VZV infection is associated with a number of risk factors, including age, immune status and a number of chronic underlying diseases, including diabetes mellitus, chronic obstructive pulmonary disease, rheumatoid arthritis and systemic lupus erythematosus (44).

The present study also examined indicators related to rheumatic immunity, and there were no abnormal indicators related to disease. Chest CT was completed in this patient, and no COPD was found. Detailed screening for some of the aforementioned risk factors was not performed in the treatment of the present patient. According to a previous meta-analysis, the overall risk of developing shingles in patients with diabetes mellitus is 1.6X higher compared with that in patients without diabetes mellitus (45). Therefore, monitoring and control of blood sugar is necessary. Patients with diabetes mellitus bring difficulties to treatment. The present patient's blood glucose monitoring did not meet the criteria for diabetes. If a VZV infected patient has diabetes while taking glucocorticoids it will raise blood glucose levels, then the increase in blood glucose will decrease the effect of treatment. For the treatment of this disease, glucocorticoids are necessary, and it would promote the increase of blood glucose. This forms a vicious circle, whereby if the increase in blood glucose is severe, glucose-lowering medications may be added as the next step for faster recovery. For patients with VZV infection and diabetes, it is recommended to perform regular monitoring of fasting and postprandial 2-h finger blood glucose levels upon admission. Based on the results of glucose monitoring, insulin preparations should be administered to correct the condition and ensure that the patient's blood glucose remains within a normal range, thereby preventing any impediment in the recovery process caused by abnormal blood glucose levels.

It has also been reported that CSF protein and serum procalcitonin levels are potential markers for differentiating bacterial from viral meningitis, where their combinations conferred higher predictive accuracy to bacterial meningitis. No one marker is better than the other, but it is easier to determine the nature of the disease if these two test results either increase together or decrease together (46). However, the present study only tested CRP without testing procalcitonin (PCT). PCT would usually be tested if the fever lasts for >5 days (47), whereas the present patient had only been running a fever for 3 days after admission and we felt that the cost of measuring procalcitonin was relatively high. Moreover, it would not significantly impact the treatment plan. Therefore, in order to save costs for the patient, we did not proceed with further testing of procalcitonin. Both CRP and PCT should be tested in subsequent clinical analyses of patients exhibiting similar characteristics. In addition, it is also necessary to see the cerebrospinal fluid color, cell number and the proportion of neutrophils. Generally, the cerebrospinal fluid color of viral encephalitis is colorless and transparent, and the color of bacterial infection will have turbidity or color change. If the cerebrospinal fluid white blood cell number is $>10x10^6$/l, and the proportion of neutrophils is >50%, then bacterial infection or secondary bacterial infection after viral infection should be suspected (48). Although cerebrospinal fluid NGS did not find bacterial infection, we should not rely too much on the auxiliary examination results and antimicrobial treatment should be given in time.

At present, most of the literature on the treatment of VZV central nervous system infection still discusses antiviral and glucocorticoid therapy (13,49), Antiviral drugs (50) include acyclovir, valacyclovir and famciclovir (FDA-approved drug for the treatment of VZV infection), brivudine (used in some European countries), and anamivir (helicase-primer inhibitor, approved in Japan). These antiviral drugs have a certain effect, but the effect on postherpetic pain is poor, and new antiviral drugs still need to be further developed (51). Prevention of VZV infection by vaccination or passive immunization is well established in medical practice (49). The present patient was not vaccinated, and novel antiviral agents were not available at this institution, which contributed to the treatment we did not expect for this patient.

VZV infection may be associated with some potential confounding factors, which will affect the clinical manifestations and outcomes of the disease. A Japanese study showed that patients with a history of herpes zoster for <10 years have half the risk of infection compared with the general population (52). The present patient did not have a history of herpes zoster infection in the last 10 years, so she was at higher risk of infection. Another study showed that hot and humid weather increases hospital visits for HZ infections, that the onset of the disease is more common in women >40 years old and the season of this patient's onset is more often in a hot and humid environment, and the age and sex of the present patient was consistent with this report (53). Further research on confounding factors for VZV infection is needed, this can prevent the occurrence of such diseases.

In conclusion, the present case documented a patient with meningitis after VZV infection, followed by peripheral facial paralysis. The clinical manifestations of VZV infection are complex and varied, which requires the clinician to have an accurate understanding of disease progression and treatment. In addition, changes in blood sugar in the patient require constant monitoring, because the incidence of herpes zoster infection is higher in patients with diabetes mellitus compared with that in general patients. If we see such patients again, we need to reduce the hormone dosage slowly for about 3 weeks, and choose the right brand of ceftriaxone. A Chinese specialist in the diagnosis and treatment of herpes zoster (35) recommends a 3-day course of corticosteroids for patients with VZV-induced meningitis, similar to the treatment received by the patient in Japan who was given 1 g of methylprednisolone intravenously. The normal protocol involves tapering off the dosage slowly to prevent exacerbation of the underlying condition. After 3 days of using 1 g, the dosage is reduced to 500 mg for another 3 days, then further reduced to 250 mg for another 3 days, followed by a reduction to 125 mg for another 3 days. After that, oral

administration begins at a dose of 60 mg and is gradually decreased over a period of three days until reaching a dose of only 15 mg before stopping completely (54). This is the standard procedure. The recommended dosage and treatment plan for methylprednisolone suggested by Chinese experts did not align with the patients' conditions, the prednisolone instructions have already stated that shock therapy should only be used for patients with severe disease deterioration or those who are unresponsive to conventional treatments such as non-steroidal anti-inflammatory drugs, gold salts and penicillamine (55). The present patient showed improvement with regular treatment, resulting in no fever and a change from unconsciousness to alertness. The present study considered this treatment to be effective, so there is no need for shock therapy with methylprednisolone. There are also a number of adverse reactions associated with shock therapy, such as masking infections, electrolyte imbalances and avascular necrosis of the femoral head. As doctors, we should always consider treatment plans that provide more benefits than risks for our patients. Nevertheless, we are inclined to believe that this protocol holds potential for treating individuals afflicted with VZV-induced meningitis. As for the use of ceftriaxone sodium (Rocephin), the present study found it to be more effective than other brands in treating high fever associated with this type of infection. Hence, we hypothesize that, for severe cases, after an initial high-dose corticosteroid treatment followed by gradual tapering off, ceftriaxone sodium could be chosen as an effective option specifically targeting signs of intracranial infection.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author. The corresponding datasets have been submitted to a public database (National Center of Biotechnology Information; accession no. PRJNA1123841; https://dataview.ncbi.nlm.nih.gov/object/PRJNA1123841?reviewer=8i43p9hgrn6gpvf0rim02k5uac).

Authors' contributions

YH, MZ, MH and LZ contributed to the conception of this article. Discussion and analysis were performed by LZ. YH and MZ wrote the first draft of the manuscript. MH and YH confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient was informed that data concerning the case would be submitted for publication and consented.

Competing interests

The authors declare that they have no competing interests.

References

1. Gnann JW and Whitley J: Neurologic manifestations of varicella and herpes zoster. Scheld WM, Whitley RJ and Marra CM, (eds): In: Infections of the central nervous system. 3rd edition. Lippincott Williams & Wilkins, Philadelphia, pp145-157, 2004.
2. Cohen JI: The varicella-zoster virus genome. Curr Top Microbiol Immunol 342: 1-14, 2010.
3. Arvin AM: Varicella-zoster virus. Clin Microbiol Rev 9: 361-381, 1996.
4. Vleck SE, Oliver SL, Brady JJ, Blau HM, Rajamani J, Sommer MH and Arvin AM: Structure-function analysis of varicella-zoster virus glycoprotein H identifies domain-specific roles for fusion and skin tropism. Proc Natl Acad Sci USA 108: 18412-18417, 2011.
5. Zerboni L, Sen N, Oliver SL and Arvin AM: Molecular mechanisms of varicella zoster virus pathogenesis. Nat Rev Microbiol 12: 197-210, 2014.
6. Ayoade F and Kumar S: Varicella-Zoster Virus (Chickenpox). In: StatPearls. StatPearls Publishing, Treasure Island, FL, 2022.
7. Gershon M and Gershon A: Varicella-Zoster virus and the enteric nervous system. J Infect Dis 218 (Suppl 2): S113-S119, 2018.
8. Cunningham AL and Heineman T: Vaccine profile of herpes zoster (HZ/su) subunit vaccine. Expert Rev Vaccines 16: 1-10, 2017.
9. Kennedy PGE and Gershon AA: Clinical features of Varicella-Zoster virus infection. Viruses 10: 609, 2018.
10. Tiwaskar M and Vora A: Unveiling the uncertainties: Exploring the utility of herpes zoster vaccines. J Assoc Physicians India 71: 11-12, 2023.
11. Patil A, Goldust M and Wollina U: Herpes zoster: A review of clinical manifestations and management. Viruses 14: 192, 2022.
12. Nagel MA, Forghani B, Mahalingam R, Wellish MC, Cohrs RJ, Russman AN, Katzan I, Lin R, Gardner CJ and Gilden DH: The value of detecting anti-VZV IgG antibody in CSF to diagnose VZV vasculopathy. Neurology 68: 1069-1073, 2007.
13. Nagel MA, Niemeyer CS and Bubak AN: Central nervous system infections produced by varicella zoster virus. Curr Opin Infect Dis 33: 273-278, 2020.
14. Harbecke R, Cohen JI and Oxman MN: Herpes Zoster vaccines. J Infect Dis 224 (Suppl 2): S429-S442, 2021.
15. Werner RN and Ghoreschi K: Herpes zoster-prevention, diagnosis, and treatment. Hautarzt 73: 442-451, 2022.
16. Shikova E, Kumanova A, Tournev I, Zhelyazkova S, Vassileva E, Ivanov I and Pishmisheva M: Varicella zoster virus infection in neurological patients in Bulgaria. J Neurovirol 27: 272-278, 2021.
17. de Ory F, Avellón A, Echevarría JE, Sánchez-Seco MP, Trallero G, Cabrerizo M, Casas I, Pozo F, Fedele G, Vicente D, *et al*: Viral infections of the central nervous system in Spain: A prospective study. J Med Virol 85: 554-562, 2013.
18. Nagel MA and Gilden D: Neurological complications of varicella zoster virus reactivation. Curr Opin Neurol 27: 356-360, 2014.
19. Liu Q, Zhou X and Li Z: Acute myelitis with multicranial neuritis caused by Varicella zoster virus: A case report. BMC Neurol 22: 45, 2022.
20. Heckmann JG, Lang C, Urban P, Glocker FX, Weder BJ, Reiter G, Bischoff C, Meier U and Guntinas-Lichius O: Therapie der idiopathischen Fazialisparese (Bell's palsy). Akt Neurol 44: 712-727, 2017.
21. Heckmann JG, Urban PP, Pitz S, Guntinas-Lichius O and Gágyor I: The diagnosis and treatment of idiopathic facial paresis (Bell's Palsy). Dtsch Arztebl Int 116: 692-702, 2019.
22. Holman AE and Puglia MP II: Loss of corneal reflex in children undergoing spinal anesthesia: A case series. A A Pract 14: 9-11, 2020.
23. Warner MJ, Hutchison J and Varacallo M: Bell Palsy. In: StatPearls. StatPearls Publishing, Treasure Island, FL, 2023.
24. Kim SJ and Lee HY: Acute peripheral facial palsy: Recent guidelines and a systematic review of the literature. J Korean Med Sci 35: e245, 2020.

25. Takami K, Kenzaka T, Kumabe A, Fukuzawa M, Eto Y, Nakata S, Shinohara K and Endo K: Varicella-zoster virus-associated meningitis, encephalitis, and myelitis with sporadic skin blisters: A case report. World J Clin Cases 10: 717-724, 2022.
26. Muñoz-Sellart M, García-Vidal C, Martínez-Yelamos S, Niubó J and Fernández-Viladrich P: Peripheral facial palsy after varicella.Report of two cases and review of the literature. Enferm Infecc Microbiol Clin 28: 504-508, 2010.
27. Hakami MA, Khan FR, Abdulaziz O, Alshaghdali K, Hazazi A, Aleissi AF, Abalkhail A, Alotaibi BS, Alhazmi AYM, Kukreti N and Binshaya AS: Varicella-zoster virus-related neurological complications: From infection to immunomodulatory therapies. Rev Med Virol 34: e2554, 2024.
28. Tavazzi E, Minoli L, Ferrante P, Scagnelli P, Del Bue S, Romani A, Ravaglia S and Marchioni E: Varicella zoster virus Meningo-encephalo-myelitis in an immunocompetent patient. Neurol Sci 29: 279-283, 2008.
29. Ottaiano AC, Gomez GD and Freddi TAL: The facial nerve: Anatomy and pathology. Semin Ultrasound CT MR 44: 71-80, 2023.
30. Liu H, Wang J, Zhang Y, Gu J, Wang Y, Yan Y, Pan D and Sun Z: Cerebrospinal fluid proteomics in meningitis patients with reactivated varicella zoster virus. Immun Inflamm Dis 11: e1038, 2023.
31. Lind L, Eriksson K and Grahn A: Chemokines and matrix metalloproteinases in cerebrospinal fluid of patients with central nervous system complications caused by varicella- zoster virus. J Neuroinflammation 16: 42, 2019.
32. Tunkel AR, Glaser CA, Bloch KC, Sejvar JJ, Marra CM, Roos KL, Hartman BJ, Kaplan SL, Scheld WM and Whitley RJ; Infectious Diseases Society of America: The management of encephalitis: Clinical practice guidelines by the infectious diseases society of America. Clin Infect Dis 47: 303-327, 2008.
33. Siciliano V, Rosà T, Del Vecchio P, D'Angelillo A, Brigida M, Longhitano Y, Zanza C, Santoro MC, Candelli M, Franceschi F and Piccioni A: Viral encephalitis in adults: A narrative review. Rev Recent Clin Trials 17: 259-267, 2022.
34. Hongo T, Ikeda F, Fujioka S, Akatsuka R, Fujiwara T and Yamamoto K: Intravenous Vitamin C as ancillary treatment for cranial polyneuritis and meningitis due to varicella zoster virus reactivation. Acta Med Okayama 74: 257-260, 2020.
35. Chinese Medical Association Dermatologists' Subcommittee on Herpes Zoster Expert Consensus Working Group. Chinese consensus on the diagnosis and management of herpes zoster (2022). Chin J Dermatol 55: 1033-1040, 2022.
36. Shahkarami F, Fallah Tafti M, Alizadeh M, Foroughi A and Bayati R: An unusual case of Group B streptococcal meningitis with concomitant varicella-zoster virus infection in a previously healthy male. Cureus 14: e32134, 2022.
37. Amlie-Lefond C and Gilden D: Varicella zoster virus: A common cause of stroke in children and adults. J Stroke Cerebrovasc Dis 25: 1561-1569, 2016.
38. Murala S, Nagarajan E and Bollu PC: Infectious causes of stroke. J Stroke Cerebrovasc Dis 31: 106274, 2022.
39. Gilden D: Varicella-Zoster virus infections. Continuum (Minneap Minn) 21: 1692-1703, 2015.
40. Muñoz-Quiles C, López-Lacort M, Ampudia-Blasco FJ and Díez-Domingo J: Risk and impact of herpes zoster on patients with diabetes: A population-based study, 2009-2014. Hum Vaccin Immunother 13: 2606-2611, 2017.
41. Papagianni M, Metallidis S and Tziomalos K: Herpes zoster and diabetes mellitus: A review. Diabetes Ther 9: 545-550, 2018.
42. Verma VK, Ram VS, Singh PS, Kumar M, Awasthi S and Kela D: Herpes zoster as a presentation of diabetes mellitus. Int J Res Med Sci 5: 1878-1881, 2017.
43. Odhaib SA and Mansour A: Herpes zoster infection as a presentation for hidden diabetes mellitus. Cureus 12: e7363, 2020.
44. Koshy E, Mengting L, Kumar H, Somagond YM, Priyadarsini S, Kuniyal A, Prakash V and Sahoo A: Epidemiology, treatment and prevention of herpes zoster: A comprehensive review. Indian J Dermatol Venereol Leprol 84: 251-262, 2018.
45. Lai SW, Liu CS, Kuo YH, Lin CL, Hwang BF and Liao KF: The incidence of herpes zoster in patients with diabetes mellitus: A meta-analysis of cohort studies. Medicine (Baltimore) 100: e25292, 2021.
46. Alnomasy SF, Alotaibi BS, Mujamammi AH, Hassan EA and Ali ME: Microbial aspects and potential markers for differentiation between bacterial and viral meningitis among adult patients. PLoS One 16: e0251518, 2021.
47. Hu L, Shi Q, Shi M, Liu R and Wang C: Diagnostic value of PCT and CRP for detecting serious bacterial infections in patients with fever of unknown origin: A systematic review and Meta-analysis. Appl Immunohistochem Mol Morphol 25: e61-e69, 2017.
48. Shahan B, Choi EY and Nieves G: Cerebrospinal fluid analysis. Am Fam Physician 103: 422-428. 2021.
49. Sauerbrei A: Diagnosis, antiviral therapy, and prophylaxis of varicella-zoster virus infections. Eur J Clin Microbiol Infect Dis 35: 723-734, 2016.
50. Yaldiz M, Solak B, Kara RO, Cosansu N and Erdem MT: Comparison of famciclovir, valaciclovir, and brivudine treatments in adult immunocompetent patients with herpes zoster. Am J Ther 25: e626-e634, 2018.
51. Andrei G and Snoeck R: Advances and perspectives in the management of varicella-zoster virus infections. Molecules 26: 1132, 2021.
52. Kawahira K, Imano H, Yamada K, Mori Y, Asada H, Okuno Y, Yamanishi K and Iso H: Risk of herpes zoster according to past history in the general population: The Japanese Shozu herpes zoster study. J Dermatol 50: 1140-1144, 2023.
53. Lv X, Fang X, Qian T, Cai Y, Gao P, Chen H, Wu Q, Wu J, Fan Y and Ye D: Association between meteorological factors and outpatient visits for herpes zoster in Hefei, China: A Time-Series analysis. Int J Environ Res Public Health 20: 2097, 2023.
54. Sinha A and Bagga A: Pulse steroid therapy. Indian J Pediatr 75: 1057-1066, 2008.
55. Pikkel YY and Pikkel J: Acute retinal necrosis in childhood. Case Rep Ophthalmol 5: 138-143, 2014.