Open Access

SCHOLARENA

Journal of Microbiology and Laboratory Science

CASE SERIES

Diagnosis of Varicella Zoster Virus Meningitis/Meningoencephalitis by the Meningitis Encephalitis Panel That Detects DNA by PCR: A Case Series

Galloza-Rivera SD and Khardori N*

Eastern Virginia Medical School, Norfolk, Virginia, United States

***Corresponding author:** Khardori N, Eastern Virginia Medical School, Norfolk, Virginia, United States, Tel: 757-446-8999, E-mail: khardonm@evms.edu

Citation: Galloza-Rivera SD, Khardori N (2018) Diagnosis of Varicella Zoster Virus Meningitis/Meningoencephalitis by the Meningitis Encephalitis Panel That Detects DNA by PCR: A Case Series. J Microbiol Lab Sci 1: 103

Article history: Received: 30 April 2018, **Accepted:** 26 July 2018, **Published:** 30 July 2018

Abstract

Varicella Zoster Virus (VZV) is an unusual cause of meningitis/meningoencephalitis in healthy population. We report three cases in which the diagnosis of *VZV* meningitis/meningoencephalitis was made by the Meningitis Encephalitis Panel (MEP) for deoxyribonucleic acid (DNA) by polymerase chain reaction (PCR).

Keywords: *Varicella Zoster Virus;* Meningitis; Meningoencephalitis

Introduction

Human alphaherpes virus 3 or VZV is a neurotropic herpes virus that infects exclusively humans [1-3]. Primary infection causes varicella after which the virus remains latent in cranial and dorsal root ganglia. Reactivation of *VZV* causes herpes zoster (shingles), but has also been associated with a number of neurological complications, including encephalitis, meningitis, post-herpetic neuralgia, and myelitis [1-8]. These manifestations are often preceded by the development of a rash in the dermatome involved and usually affect older individuals and/or immunocompromised patients [1-8]. Meningitis and meningoencephalitis are uncommon complications of *VZV* infection. In a report of 859 patients with *VZV* infection; meningitis was reported in only 0.5% within 60 days of diagnosis [4,8]. However, latest epidemiological studies found a portion of *VZV* in 5-29% of aseptic meningitis and encephalitis by using sensitive laboratory studies (e.g. , PCR, detection of intrathecal production of specific antibodies); suggesting that *VZV* infections had been underrated in prior publications [1,4]. Incidence increases with age i.e 2.5/1000 in ages 21-50 versus 10.1 cases/1000 in patients older than 80 years [4]. A definitive diagnosis of central nervous system (CNS) infection with *VZV* require the demonstration of *VZV* DNA in cerebrospinal fluid (CSF), or the presence of anti-*VZV* IgG antibody in CSF or anti-*VZV* IgM antibody in CSF and/or serum [2,4].

Here, we present three cases in which the diagnosis of *VZV* meningitis/meningoencephalitis was made using the commercially available MEP for detection of DNA by PCR. This includes DNA testing for *Escherichia coli K1, Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitides (encapsulated), Streptococcus agalactiae, Streptococcus pneumoniae, Cytomegalovirus, Enterovirus, Herpes simplex virus (HSV) 1, HSV 2, Human herpesvirus 6, Human parechovirus, VZV, and Cryptococcus neoformans/gattii*, and is used mostly for diagnosis in pediatric patients [9].

PCR is an inexpensive, rapid, and highly sensitive method of detecting herpes viruses, and its development has made diagnosis of neurologic disease related to *VZV* much easier [3,9]. In this report we emphasize the applicability of the MEP for DNA by PCR as a useful tool for the diagnosis of *VZV* CNS infections in the adult population, and encourage its widespread use.

Methodology

This case series was based on review of electronic medical records from patients diagnosed with *VZV* meningitis/meningoencephalitis.

We included all patients admitted to the Sentara Norfolk General Hospital, Norfolk, VA diagnosed with *VZV* meningitis/meningoencephalitis in 2016 and 2017. A total of three patients meet the criteria.

A literature review is also included. An English-language literature search was conducted of the PubMed databases using search terms '*VZV* meningitis/meningoencephalitis', 'neurologic complications of *VZV*', '*VZV* and CNS disease'.

The diagnosis of *VZV* meningitis/meningoencephalitis was made by using the MEP for DNA by PCR available at the nearby Children's Hospital of the Kings Daughter. The MEP is a commercially available FDA-approved FilmArray panel for viruses, bacteria, and yeast manufactured by BioFire, a Biomerieux Company. It is a designed comprehensive panel that combines a broad grouping of probable pathogenic causes into a single, rapid test using DNA by PCR.

Case 1

59 year old male presented to the emergency department (ED) with four day history of confusion, ataxia, and headache. Wife noted over the previous four days the patient had worsening headache, fatigue, confusion and unstable gait without falls. Patient had presented to an outside hospital two days prior to admission with same complaints and was given azithromycin for sinusitis. Symptoms did not improve, and patient was brought to our teaching hospital due to worsening mental status. Wife informed us that five days prior he was working with "Terro" ant spray, and reported spraying himself in the face. He gave no history of seizures, meningitis, drug use, but used alcohol many years ago. There was no nausea, vomiting, diarrhea, fever or chills at presentation.

His medical history was significant for diabetes mellitus type 2 managed by insulin, hypothyroidism, and recently treated for Hepatitis C with excellent response. Patient reported spending a lot of time outdoors, had no pets, and traveled to Caribbean one year ago.

On day 2 of hospitalization patient developed a witnessed tonic-clonic seizure and was transferred to intensive care unit (ICU). He was intubated for airway protection. Following transfer to the ICU, he underwent a guided spinal tap by interventional radiology. Patient was started on vancomycin, ceftriaxone and acyclovir for presumptive treatment. Neurology was consulted for seizures. He was placed on intravenous (IV) Keppra and Fosphenytoin.

Cerebrospinal fluid (CSF) findings were as follows: white blood cell (WBC) count 682 cells/μL (lymphocyte 94%, neutrophil 1%), protein 287.2 mg/dL, glucose 63 mg/dL and opening pressure 29 cm H_2O.

Computed Tomography (CT) scan of brain did not reveal any abnormalities. Magnetic Resonance Imaging (MRI) of brain showed two nodular foci of cortical enhancement in right occipital lobe consistent with artifact, vascular malformation, or malignancy.

Doxycycline was started for the concern of recent tick bite. Infectious disease was consulted and ampicillin was added. The PCR for *HSV 1 and HSV 2* in the CSF was negative, but acyclovir was continued because we had sent the spinal fluid for the MEP available at a nearby hospital.

Admission and repeat blood cultures did not show any bacterial or fungal growth. Further CSF studies showed no evidence of bacterial meningitis, which led to discontinuation of vancomycin, ampicillin and ceftriaxone. However, on the fifth day of hospitalization the MEP revealed *VZV* DNA by PCR. Acyclovir was continued with significant improvement in mental and overall status. IV Keppra and Fosphenytoin were eventually transitioned to oral regimen. Neurology recommended he stay on both for three months and follow up with them as an outpatient.

Tick-borne serologies (*Ehrlichia, Anaplasma, Lyme disease*) returned negative. At that point doxycycline was also discontinued.

High dose IV acyclovir was continued for a total of 14 days, completed at home. Patient was seen in follow up in infectious disease clinic 2 weeks later and found to have complete resolution of his symptoms.

Case 2

19 year old female with medical history of gastroesophageal reflux and chronic pain presented with rash and swelling on the right side of forehead and right eye pain. The rash started one week prior to admission. She was initially diagnosed with streptococcal pharyngitis and poison ivy and was given keflex and prednisone. However, rash and pain continued to worsen. She went back to primary care physician for continued headache along with progressing rash, and was referred to the ED.

Patient was seen by ophthalmology and admitted to our teaching hospital with fever, headache and neck stiffness in addition to possible herpes virus conjunctivitis.

Of note, patient was in Guatemala two months prior and had contact with girls who had chicken pox.

Patient herself did not get chicken pox as a child, but had been vaccinated.

On physical examination she was afebrile and in no acute distress. She had vesicular lesions on right forehead and right side of the scalp, some were crusted. Spinal fluid showed WBC count 30 cells/μL (lymphocytes 84%, neutrophils 2%), protein 33 mg/dL and glucose of 55 mg/dL. She was started on vancomycin, ceftriaxone and acyclovir. CSF cultures returned negative and vancomycin and ceftriaxone were discontinued. PCR for *HSV 1 and 2* was negative. PCR for *VZV* was positive by MEP testing. She was continued on high dose IV acyclovir to complete a total of 14 days.

Patient had recurrent positional headache after the spinal tap due to CSF leak. This was repaired by blood patch placement with improvement in headache.

Patient was followed by ophthalmology while hospitalized, there was no intraocular involvement. She was placed on topical erythromycin, and followed as outpatient.

Rash improved and she was discharged on gabapentin for neuropathic pain.

Case 3

60 year old male was admitted with new left-sided weakness, slurred speech and gait changes since that morning. Initial CT scan of head was negative for acute process. MRI showed acute infarct in the right and central pons and two small foci of abnormal signal in the pons, suggesting tiny areas of probable interval petechial hemorrhage.

Patient had been diagnosed with chronic lymphocytic meningitis four months ago with initial presentation of anisocoria; large right pupil. Patient had two spinal fluid examinations with negative results for a microbiologic etiology. Spinal fluid # 1 showed WBC count 354 cells/μL (lymphocytes 97%, monocytes 3%), protein 295 mg/dL, glucose 33 mg/dL; and spinal fluid # 2 WBC count 204 cells/μL (lymphocytes 52%, monocytes 47%), protein 189 mg/dL, glucose 35 mg/dL. He was discharged home, but continued to have headache, mild dizziness and intermittent diplopia persisting till the current admission.

Past medical history was significant for hyperlipidemia, psoriasis, multiple cranial nerve neuropathy; including bilateral optic neuropathy, right eye pupillary abnormality, left vocal cord paralysis, hearing and vestibular symptoms with antinuclear antibody, c reactive protein and erythrocyte sedimentation rate having been normal.

Physical examination showed dense left hemiplegia, clonus of left ankle, increased muscle tone on left leg, left facial palsy, dysarthria and larger pupil on right that was non-responsive to light.

The spinal fluid at this admission showed improving pleocytosis: WBC count 42 cells/μL (lymphocytes 93%, monocytes 7%) however still had low glucose 32 mg/dL and high protein 195 mg/dL. Once again all microbiological work up was negative, including PCR for HSV 1 and 2. Subsequently PCR was positive for *VZV* DNA by MEP testing. Patient stated he probably had chicken pox as a child, but no shingles as an adult. He was started on high dose IV acyclovir treatment.

MRI was reviewed with neuroradiology: subtle finding of some leptomeningeal enhancement was present at pons level. No obvious findings of *VZV* specific vasculitis were noted.

Quantiferon TB-Gold and CSF *Mycobacterium tuberculosis* PCR were both negative.

He developed leukopenia during the hospitalization (WBC count 1.8 cells/μL), hematology-oncology was consulted. Bone marrow biopsy was performed and showed no evidence of primary hematologic abnormality. Despite leukopenia; the patient did not appear to have experienced any adverse consequences related to this event. His WBC count recovered without specific treatment (WBC count 4.3 cells/μL), while he was continued on high dose IV acyclovir.

The admission was also complicated by acute kidney injury which improved with intravenous fluids.
Patient was transferred to the rehabilitation unit and completed 14 days of high dose IV acyclovir with some
Improvement in his motor function. Unfortunately, he was lost to follow up.

Discussion

The cases reported here point to the usefulness of early use of MEP for DNA by PCR as a point of care test for central nervous system infections in adults. If *VZV* had not been detected by this test, acyclovir might have been discontinued when the results of *HSV PCR* were reported to be negative. Our cases emphasize the importance of specialized CSF studies in acute neurological presentations. CSF examination is considered a vital method in the diagnosis of CNS infections using sensitive laboratory tests (e.g. PCR and intrathecal *VZV* IgG and IgM antibodies) [1,2,4]. Acute manifestations of *VZV* reactivation affect mainly older persons and/or patients with some degree of immunosuppression [1-8].

Klein et al. described a case of *VZV* meningoencephalitis that initially presented with the clinical picture of aseptic meningitis with a lymphocytic pleocytosis, elevated CSF protein, and a negative Gram stain, but developed onset of confusion and disorientation on hospital day 2 [3]. No rash was present over the entire hospitalization. She was started on acyclovir for presumed HSV encephalitis, and *VZV* DNA was detected in the CSF by PCR testing, as it was in our cases [3]. This patient was not known to suffer from any degree of immunosuppression. Pasedag et al. reported a young previously healthy man with *VZV* meningitis without a rash [1]. The clinical presentation was unusual for a patient with meningitis and the initial CSF findings (very high pleocytosis and elevated total CSF protein) suggested a bacterial infection, but further CSF testing detected *VZV* infection [1]. In our report, none of the patients was known to suffer from any immunocompromising condition; and two of them did not develop the typical rash associated with zoster. All of our patients were diagnosed with the MEP for DNA by PCR. If a high index of suspicion had not been present for *VZV* infections in these cases we might have missed the diagnosis.

These cases highlight the importance of considering *VZV* in the differential diagnosis of meningitis and meningoencephalitis in the normal host and in patients without a rash. Clinicians should have a high index of suspicion for *VZV* related CNS infections and must not hesitate ordering PCR for *VZV* DNA and initiating aggressive antiviral therapy early for a better patient outcome.

The MEP for DNA by PCR is a simple diagnostic test to detect *VZV* early and should be considered in all patients presenting with neurologic symptoms.

Conclusion

In patients presenting with acute neurological complaints, *VZV* must be in the differential diagnosis even in immunocompetent patients and patients who do not have a rash. The MEP is a useful and rapid test that led to the diagnosis of *VZV* CNS infections in all three of patients reported here.

References

1. Pasedag T, Weissenborn K, Wurster U, Ganzenmueller T, Stangel M, et al. (2014) Varicella Zoster Virus Meningitis in a Young Immunocompetent Adult witho ut Rash: A Misleading Clinical Presentation. Case Reports in Neurological Medicine Article ID 686218.

2. Gilden D, Cohrs RJ, Mahalingam R, Nagel MA (2010) Neurological Disease Produced by Varicella Zoster Virus Reactivation Without Rash. Curr Top Microbiol Immunol 342: 243-53.

3. Klein NC, Mcdermott B, Cunha BA (2010) Varicella-zoster virus meningoencephalitis in an immunocompetent patient without a rash. Scand J Infect Dis 42: 631-3.

4. Gupta P, Ranjan R, Agrawal CS, Muralikrshnan K, Dave N, et al. (2016) Meningitis with polymerase chain reaction for varicella zoster positivity in cerebrospinal fluid of a young immunocompetent adult. J Neurosci Rural Pract 7: 591-3.

5. Choi R, Kim GM, Jo IJ, Sim MS, Song KJ, et al. (2014) Incidence and Clinical Features of Herpes Simplex Viruses (1 and 2) and Varicella-Zoster Virus Infections in an Adult Korean Population with Aseptic Meningitis or Encephalitis. J Med Virol 86: 957-62.

6. Maria A Nagel, Don Gilden (2014) Neurological Complications of VZV Reactivation. Curr Opin Neurol 27: 356-60.

7. Spernovasilis N, Milioni A, Gialamas I, Kikirakis E, Fanti G (2018) Varicella-zoster virus meningitis with hypoglycorrhachia in a young immunocompetent adult without rash: A case report and literature review. IDCases 12: 104-6.

8. Sang-Hoon K, Seong-Min C, Byeong C. K, Kang-Ho C, Tai-seung N, et al. (2017) Risk Factors for Aseptic Miningitis in Herpes Zoater Patients. Ann Dermatol 29: 283-7.

9. FilmArray Panels, Comprehensive Panels and Better Diagnostics, BioFire, A Biomerieux Company 12-5.