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Leveraging BioFire FilmArray (Multiplex Polymerase Chain Reaction) to Unmask Varicella Zoster Virus Meningoencephalitis: A Rare Case Report of Geriatric Neuro-Infection from North India

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ABSTRACT

Meningoencephalitis typically presents with fever and signs of meningeal irritation thereby, making it difficult to distinguish bacterial, viral and fungal aetiology merely on clinical examination. Therefore, the use of multiplex PCR (Polymerase Chain Reaction) targeting multiple etiological agents enhances accurate diagnosis and shortens turn-around time. We hereby report a case of acute VZV (Varicella zoster virus) encephalitis with superadded bacterial infections in an elderly male patient diagnosed via Biofire FilmArray, in Uttarakhand region of North India.

A 69-year-old male patient presented to Emergency department of AIIMS, Rishikesh with complaints of fever, headache, projectile vomiting and altered mental sensorium from where he was admitted in General Medicine HDU (high dependency unit) with a working diagnosis of acute meningoencephalitis. Film Array meningoencephalitis (ME) panel (BioFire Diagnostics, LLC, Salt Lake City, Utah) [1] combining 14 pathogens into a single cartridge-based nested multiplex PCR was performed as a point-of-care test. Various lab investigations including CSF counts, aerobic cultures, microscopy, CSF CBNAAT, MRI, NCCT Head, EEG were also done to rule out other potential causes.

Microscopic staining analysis and cerebrospinal fluid culture were both negative. However, CSF Biofire came positive for VZV guiding precise treatment. VP (Ventriculo Peritoneal) shunt was placed in view of obstructive hydrocephalus revealed on NCCT-head. Repeated interventions like intubation, co-morbidities and geriatric age group lead to development of VAP (Ventilator Associated Pneumonia) due to super added bacterial infection for which culture guided antimicrobial therapy was given. Full course of appropriate antiviral treatment was given, and patient was discharged in a haemodynamically stable condition.

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POCT (Point of Care Test), Syndromic Diagnosis, Viral Infections

INTRODUCTION

Varicella zoster virus (VZV) is a virus of the alpha herpesvirus family that is neurotropic and has double-stranded DNA. The first exposure to this virus usually occurs in childhood, and the primary infection causes chickenpox, in which VZV becomes latent in the cranial nerve, spinal cord, and autonomic ganglia throughout the neuraxis [2].

Since the immune response to the virus is mainly mediated by T cells, reactivation usually occurs with aging or because of immunosuppression. Herpes zoster, also known as shingles, is caused by the reactivation of latent VZV in the dorsal root ganglion or trigeminal ganglion which manifests a bullous rash in the dermatomal distribution of sensory ganglia and acute neuritis [2].

VZV is one of the leading causes of infectious neurological diseases and the second leading cause of encephalitis and infectious meningitis. Mortality is 12-15%, which may be higher in immunocompromised patients. Therefore, swift diagnosis based on clinical manifestations, neurological symptoms, cerebrospinal fluid (CSF) analysis, and imaging abnormalities such as MRI (Magnetic Resonance Imaging) and CT (Computed Tomography) scans is required to adequately manage and improve patient outcome. In addition, point of care tests (POCT) such as multiplex PCR play a vital role in accurate diagnosis.

Here we present a rare case of VZV meningo-encephalitis in a geriatric patient from a tertiary care center of Uttarakhand.

CASE SUMMARY

A 69-year-old male patient presented at the Emergency of AIIMS Rishikesh with altered mental status persisting for 4 days, accompanied by recurrent episodes of projectile vomiting and a single episode of fever 6 days prior. Initially treated at a district hospital in Kotdwar with conservative management. This undocumented pyretic episode was associated with chills and rigors with pulsatile holocranial headache which was relieved by antipyretics. The patient's deteriorating condition prompted referral to a higher-level facility. On arrival, the patient exhibited altered mental status (GCS - E3V4M6), blood pressure of 126/68 mmHg, a pulse rate of 98/min, respiratory rate of 22/min, and maintained Spo2 of 96% with 2 liters of oxygen support. Physical examination revealed neck rigidity and a positive Kernig sign. Additionally, the patient presented with abdominal lesions characterized by a central crust surrounded by redness, preceded by blister formation and associated with a burning sensation suggestive of a viral etiology. An urgent NCCT scan of the head and thorax (Refer to Table 3) revealed findings consistent with non-communicating hydrocephalus, right-sided pneumothorax, and mild mediastinal displacement.

The patient was admitted to the High Dependency Unit and was initially managed for acute viral meningoencephalitis. On the third day of admission, a cerebrospinal fluid (CSF) examination was performed, and CSF Biofire [1] testing confirmed the presence of Varicella-Zoster Virus (VZV). The treatment regimen included Acyclovir, Meropenem, and Vancomycin. The patient who also had a history of hypertension and was on oral antihypertensive medications, experienced a sudden increase in blood pressure and a decline in sensorium on the fifth day of admission. Injectable anti-hypertensives were given to control blood pressure but due to persistent decline in sensorium, the patient was put on ventilatory support Consequently, he was transferred to the Medicine Intensive Care Unit for further management on the working diagnosis of acute viral meningoencephalitis with superadded bacterial infections. Neurosurgical consultation was sought, leading to the placement of an External Ventricular Drain (EVD) [Refer to Table 3] which resulted in an improvement in consciousness. Subsequently, due to a rise in blood counts and a decline in consciousness, the antiviral therapy was escalated to Ganciclovir. A repeat head CT scan) [refer to table 3] revealed an enlargement of the hydrocephalus, necessitating the insertion of a Ventriculoperitoneal (VP) shunt by the neurosurgical team. Despite the procedure, there was no notable improvement in consciousness. An MRI of the brain as [described in Figure A] and was performed, revealing a significant intraparenchymal hemorrhage in the right frontal lobe, along with subarachnoid hemorrhage in the bilateral temporal and occipital lobes, as well as communicating hydrocephalus.

CBNAAT testing was conducted to rule out tubercular meningitis, yielding a negative result. However, due to strong suspicions of tubercular meningitis and ongoing low sensorium, empirical Anti-Tubercular Therapy (ATT) was initiated. Subsequently, the patient developed an iatrogenic pneumothorax, necessitating the insertion and subsequent removal of an Intercostal Drainage (ICD). A tracheostomy was performed to facilitate long-term ventilatory support, and ventilator-associated pneumonia caused by *Klebsiella pneumoniae* was treated with antibiotics guided by culture results. An EEG was performed to investigate Non-Convulsive Status Epilepticus (NCSE), revealing indications of diffuse cerebellar dysfunction. Biofire (1) confirmed the presence of Varicella-Zoster Virus (VZV), despite the patient's stable condition. Following a weaning trial, the patient was extubated and transferred to the High Dependency Unit (HDU), where ATT was discontinued. Due to the persistent positive VZV cultures, the patient was scheduled to receive Intravenous Immunoglobulins targeting VZV. The patient's

overall condition notably improved in the subsequent days with appropriate management of bedsores and nutritional support through enteral feeding, leading to a discharge in a stable hemodynamic condition.

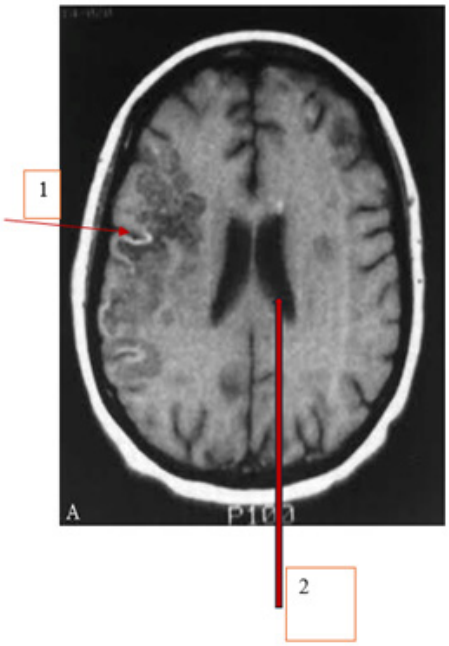

Figure A1. Sulcal hyperintensities seen along right cerebral hemispheres on T2 FLAIR MRI

Figure A2. Residual dilatation of supratentorial ventricles T2 FLAIR MRI

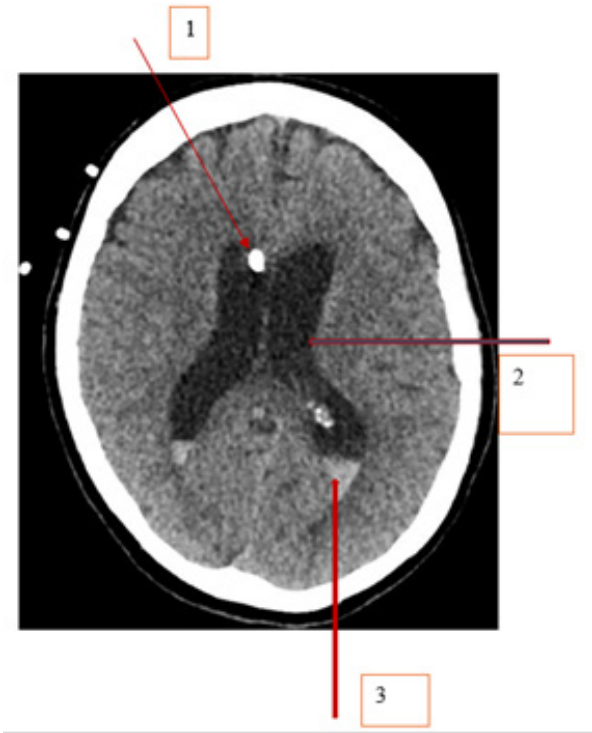

Figure B1. EVD in-situ on NCCT Head

Figure B2. Supratentorial hydrocephalus-dilatation of bilateral lateral ventricles on NCCT Head

Figure B3. Intra-ventricular haemorrhage in bilateral lateral ventricles on NCCT Head

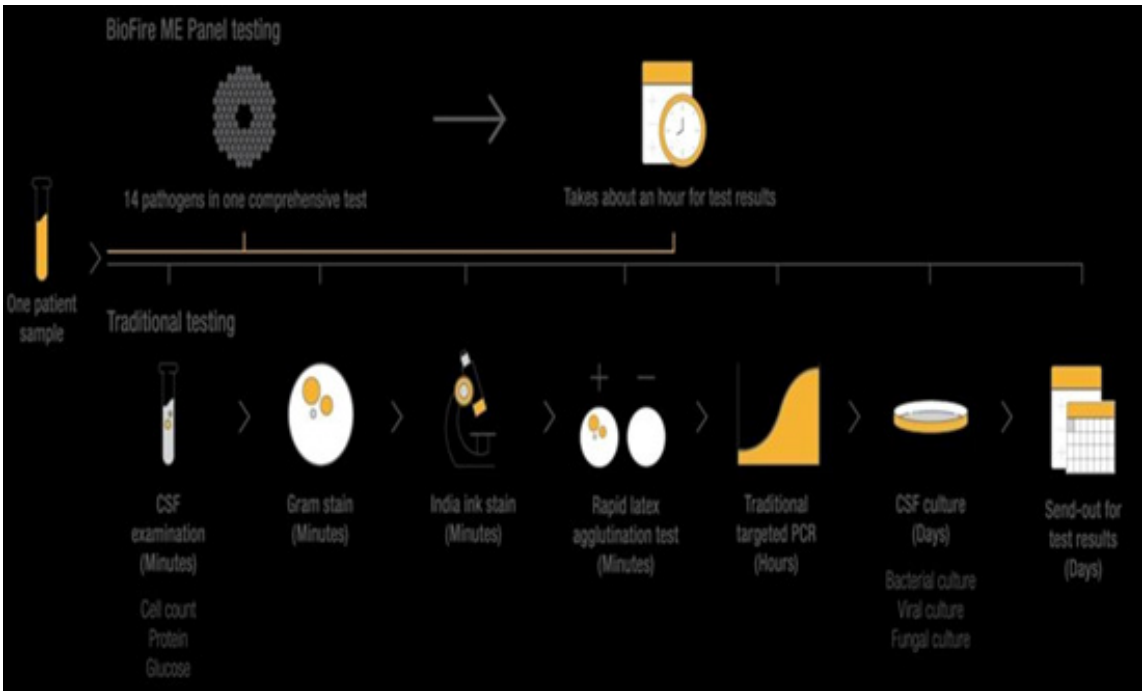

Figure C. Biofire filmarray processing (1).

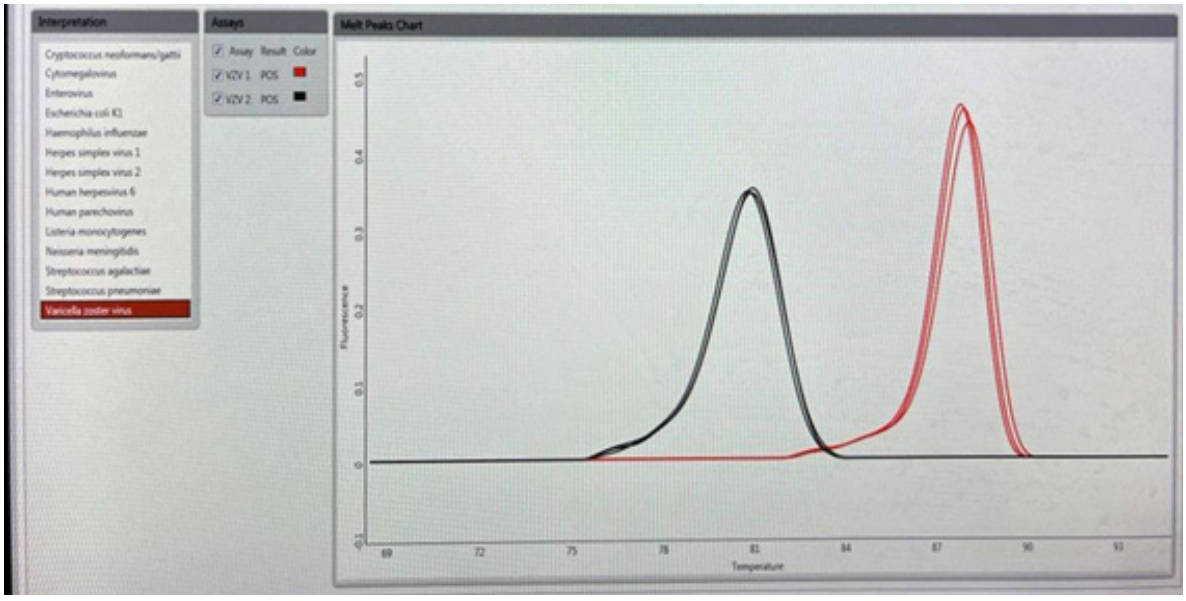

Figure D. BIOFIRE Melt curve peaks showing Varicella Zoster Virus positive.

Table 1. Hematological Investigations

INVESTIGATION	20/11/2023	22/11/2023	24/11/2023	27/11/2023	13/12/2023	18/12/2023	21/12/2023
HB	12.6	12.4	10.2	10.4	8.3	8.2	7.9
TLC (X1000)	7.41	7.1	9.12	5.93	5.45	4.43	5.6
DLC(N/L)	74.6/17.8/7.2/0.3/0.1	79.4/12.7/6.5/1.1/0.3	87/7/3	84/10/3	82/8/8	77/15/6	80/13/6
PLATELET	99k	108k	98k	112K	133 K	230K	166K

Table 2. CSF Analysis

CSF	15/11/2023	22/11/2023
TLC[1]	80	20
DLC[2]	M-70 / P- 30.	M-65 / P- 35
SUGAR/PROTIEN	86/256	88/260
CSF CULTURE	STERILE	STERILE
CBNAAT[3]	NEGATIVE	N/A
ADA[4]	3.2	N/A

ABBREVIATIONS

TLC: Total Leucocyte Count; DLC: Diffrential Leucocyte Count; CBNAAT: Cartridge Based Nucleic Acid Amplification Test; ADA: Adenosine Deaminase

Table 3. Radiological Investigations

IMAGING	FINDINGS	IMPRESSION
NCCT HEAD AND THORAX **13/11/23**	• Patchy hypodensity with a calcific focus is seen in left temporal lobe. Thalami basal ganglia, brain stem and cerebellum are normal. • Supratentorial ventricles appears dilated with periventricular ooze. The 4th ventricle appears normal. • There is no shift of the midline structures. • Bony calvanum is normal. • Visualized orbits and paranasal sinuses show no significant abnormality Nasogastric tube seen insitu with tip in stomach. **THORAX** • Right sided pneumothorax is seen of maximum depth -8.3 cm causing compressive atelectasis of the right lung. Mild mediastinal shift seen towards left side Fibro atelectatic bands with few areas of consolidation seen in collapsed lung. Few fibro atelectatic bands are seen in left lung predominantly lower zones. No bilateral pleural effusion noted Large. • Few sub centimetric mediastinal lymph nodes are seen. • Both diaphragms are normal • Atherocalcific changes are seen in aorta and its branches. • Visualised vertebrae show degenerative changes in form of osteophytes. • ET tube seen ending at level of 74 vertebra, -41cm above Carina.	• Dilated supratentorial ventricles with periventricular ooze and normal 4th ventricle- likely Non-communicating Obstructive hydrocephalus • Patchy hypodensity with a calcific focus in left temporal lobe. Advice- MRI Brain for further evaluation. **THORAX** • Right sided pneumothorax with mild mediastinal shift as detailed.

Table 4. Radiological Investigations

IMAGING	FINDINGS	IMPRESSION
NCCT HEAD 20/11/23	• Burr hole defect seen in the frontal bone on right side. • Intraparenchymal haemorrhage seen in the right parietal lobe tracking along the EVD tract with extension to the right ventricle with IVH. • SAH is seen along the sulcal spaces of bilateral temporal and occipital lobes. Mass effect is seen in the form of effacement of ipsilateral sulcal spaces. • Sulidural hygroma along right frontoparietal convexity. • There is mild dilatation of the supra and infratentorial ventricles: • Frontal horn of right lateral ventricle-16 mm Frontal born of left lateral ventricle - 15.6 mm Third ventricle-8.5 mm. • Fourth ventricle-14 x 11 mm. • Evans Index-0.31 • There is no shift of the midline structures. • Bilateral basal ganglia and thalami are normal. • Bilateral cerebellar hemispheres are normal. • Visualised orbits do not show any significant abnormality. • NG tube seen insitu. • Polypoidal thickening seen in the bilateral maxillary sinuses	• SAH is seen along the sulcal spaces of bilateral temporal and occipital lobes

Table 5. Radiological Investigations

IMAGING	FINDINGS	IMPRESSION
MRI BRAIN 28/11/23	• VP shunt is seen insitu with its tip in left lateral ventricle abutting the septum pellucidum. • An area of T1 T2 and FLAIR hyperintensity with peripheral blooming on GRE and surrounding oedema is seen in right frontal lobe, centrum semiovale, corona radiata, external capsule and basal ganglia region extending to right temporal lobe suggestive of late subacute haemorrhage. Similar area is also noted along right medial temporal lobe. IVH is seen in occipital horn of bilateral lateral ventricles (right> left) Blooming is seen along the tract of previous EVD in right frontal lobe on GRE sequence. • Supratentorial ventricular system dilatation is seen (Evan's index -0.39) • Frontal horn of right lateral ventricle-13.3 mm. • Frontal horn of left lateral ventricle -15.1 mm,3 ventricle-9 mm. • Small area of T2/FLAIR hyperintensity is seen in left centrum semiovale with diffusion restriction on DWI-Infarct. Sulcal spaces are prominent in bilateral frontal region suggestive of frontal atrophy. • Leptomeningeal enhancement is seen along bilateral cerebral hemispheres. Exudates seen along right Sylvian fissure. Rest of the bilateral cerebral hemispheres appear normal Grey white matter differentiation is maintained Brainstem, cerebellum, thalami are normal in signal intensity. • Pituitary and Sella are normal. Note made of T2/FLAIR hyperintensity in bilateral maxillary & ethmoid sinus and bilateral mastoid air cells.	• In a known case of meningitis, • Late subacute haemorrhage involving right frontal lobe, centrum semiovale, corona radiata, external capsule and basal ganglia region extending to right temporal lobe with mild. • Small infarct in left centrum semiovale.

DISCUSSION

Varicella-Zoster Virus (VZV) accounts for approximately 8-13% of all viral meningitis cases. While meningitis is a relatively uncommon manifestation of VZV, occurring in just 0.5% of infections, it remains a recognized complication [3]. Advanced age and immunocompromised states are thought to be key risk factors for the development of herpes zoster and other VZV reactivation symptoms [3] A dermatomal rash and neuritis are the most prevalent symptoms.

In this case, the patient presented with altered mental status for four days, along with recurrent vomiting and a previous episode of fever, indicating a potential diagnosis of acute meningoencephalitis. According to Lizzi J et al.'s study, VZV encephalitis typically presents with symptoms such as headache, fever, vomiting, altered consciousness, and convulsions. Additionally, focal neurological deficits like hemiparesis, cranial nerve paralysis, and abnormal osteotendinous reflexes may be observed [4]. However, our patient did not exhibit focal neurological signs. The most common symptoms of VZV encephalitis include a dermatomal rash [3] and neuritis, which align with our

patient's presentation of characteristic lesions on the abdomen with a central crust, surrounding redness, vesicle formation, and a burning sensation, indicative of a VZV infection.

The adoption of BioFire Film Array meningitis/encephalitis as an initial point-of-care test has become widespread in various healthcare institutions due to its broad availability. In the case of the patient, the CSF BioFire [1] test yielded a positive result. This diagnostic panel screens for a range of pathogens, including *Escherichia coli K1, Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitidis, Streptococcus agalactiae, S. pneumoniae*, CMV, enterovirus (EV), HSV-1, HSV-2, human herpesvirus-6 (HHV-6), human parechovirus (hPeV), VZV, *Cryptococcus neoformans*, and *Cryptococcus gattii* [1]. The advantage of this test lies in its ability to rapidly identify pathogens, enabling timely initiation of treatment, which is crucial in cases of central nervous system infections [5]. Early detection of VZV through BioFire testing allowed prompt initiation of antiviral therapy for the patient. The Infectious Diseases Society of America recommends intravenous acyclovir as the treatment of choice for VZV meningoencephalitis, with ganciclovir [6] considered an alternative agent [7]. In this case, the patient was initially treated with acyclovir and later transitioned to ganciclovir based on clinical evaluation.

Pathological studies indicate that VZV encephalitis is associated with vasculopathy in both large and small vessels [8]. MRI findings typically reveal ischemic or haemorrhagic infarctions in Gray and white matter, particularly at gray-white matter junctions, which are characteristic of VZV encephalitis. The MRI of the patient showed subacute haemorrhage involving the right frontal lobe, centrum semiovale, corona radiata, external capsule, basal ganglia region, extending to the right temporal lobe, with a mild small infarct in the left centrum semiovale.

Although the reason for the persistently positive VZV Biofire [1] could not be definitively determined, it led to the escalation of antiviral therapy and the consideration of Immunoglobulins against VZV. One plausible explanation could be polymicrobial sepsis in the patient, as evidenced by positive cultures for *Pseudomonas aeruginosa, MR-Coagulase negative staphylococci, A. baumannii, Candida,* and *Klebsiella pneumoniae*, further compromising the patient's immune status and potentially resulting in VZV shedding in CSF. The appropriate use of diagnostic tools like BioFire Film Array and targeted antiviral and antibiotic therapy contributed to the improvement of the patient's overall condition in this uncommon case of geriatric neuroinfection.

CONCLUSION

This case report underscores the significance of BioFire FilmArray in diagnosing Varicella-Zoster Virus (VZV) meningoencephalitis, a rare but potentially life-threatening condition, particularly in geriatric patients. The patient's presentation with altered mental status, vomiting, and fever, accompanied by characteristic VZV lesions, led to the suspicion of VZV infection. In addition to documenting an unusual presentation of positive Varicella zoster virus result on a meningitis/encephalitis panel, this case also emphasises the role of Biofire Filmarray as a Point of Care Test.

This multiplex PCR test confirmed the diagnosis, enabling prompt initiation of antiviral therapy. Imaging studies, including MRI and NCCT head, revealed characteristic features of VZV encephalitis, such as subacute haemorrhage and infarctions, as well as non-communicating obstructive hydrocephalus. EEG findings indicated generalized cerebral dysfunction. The patient's condition improved with targeted antiviral and antibiotic therapy, highlighting the importance of timely diagnosis and treatment in complex neuroinfections.

The unique ability of Biofire ensures identification of rare etiological agents which are difficult to diagnose conventionally. This case provides insights into how we can collaboratively enhance accuracy between various diagnostic modalities along with the use of clinical acumen, ultimately improving patient outcomes in cases of meningoencephalitis.

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