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A Complex Case of Febrile Illness in an Elderly Male with Neurological Symptoms and Negative Csf Cytopathology: A Diagnostic and Management Challenge

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ABSTRACT

An elderly male in his eighties presented with persistent high-grade fever, altered mental status, and features suggesting central nervous system (CNS) involvement. The clinical picture was concerning for infectious or inflammatory encephalopathy. The diagnostic workup included cerebrospinal fluid (CSF) analysis, cartridge-based nucleic acid amplification test (CBNAAT), line probe assay (LPA), cytopathology, fungal microscopy, and aerobic culture. Despite significant systemic symptoms, CSF analyses returned negative for tuberculosis, fungal infection, and malignant cytology. MRI and MR spectroscopy findings revealed pontine hyperintensities and metabolic abnormalities suggestive of neuronal dysfunction. The imaging also showed decreased N-acetylaspartate (NAA) and elevated choline, with a lactate peak—findings supportive of encephalopathy or inflammatory pathology. Treatment was initiated empirically with broad-spectrum antibiotics, antifungals, and supportive neurological and systemic care. Electrolyte imbalance and hypertension were addressed promptly. Despite extensive diagnostics, no specific pathogen was identified, and the patient's clinical course required close multidisciplinary monitoring. The case exemplifies the diagnostic and therapeutic challenges posed by febrile encephalopathy in the elderly, where overlapping features of metabolic, infectious, and vascular etiologies complicate definitive diagnosis. This report highlights the role of advanced imaging and CSF analysis in guiding management when primary infectious markers are inconclusive. Further follow-up, especially with culture data and clinical evolution, remains essential for ongoing care.

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Introduction

Elderly patients presenting with febrile encephalopathy pose a significant diagnostic challenge due to the vast range of potential infectious, metabolic, vascular, and neoplastic causes. Central nervous system (CNS) infections often exhibit non-specific clinical symptoms in older individuals, and the classical triad of fever, neck stiffness, and altered consciousness may be absent or attenuated [1]. Furthermore, immunosenescence and pre-existing comorbidities contribute to atypical presentations and higher morbidity and mortality in this age group [1].

Febrile encephalopathy in the elderly is a complex clinical syndrome characterized by the presence of fever and altered mental status. The incidence of CNS infections increases with age, and the clinical manifestations are often atypical. For instance, elderly patients may present with subtle signs such as confusion, lethargy, or a decline in functional status, rather than the classic symptoms observed in younger populations. This atypical presentation can lead to delays in diagnosis and treatment, thereby increasing the risk of adverse outcomes [2].

Immunosenescence refers to the gradual deterioration of the immune system associated with aging. This process affects both the innate and adaptive immune responses, leading to increased susceptibility to infections, a higher prevalence of chronic inflammatory conditions, and a diminished response to vaccinations. The decline in immune function is characterized by reduced production of naïve T and B cells, impaired function of existing immune cells, and an increase in pro-inflammatory cytokines, a phenomenon known as "inflammaging" [3,4].

Diagnosing febrile encephalopathy in the elderly is fraught with challenges. The non-specific nature of symptoms, coupled with the presence of multiple comorbidities, can obscure the clinical picture. Laboratory investigations may yield inconclusive results, and imaging studies might not always provide definitive answers. For example, cerebrospinal fluid (CSF) analysis may not reveal the presence of pathogens, and imaging findings can be subtle or non-specific [5].

In this case report, we describe an elderly male who presented with fever and neurological decline, but whose diagnostic workup yielded negative results for tuberculosis, fungal infections, and malignancy. The complexities of such diagnostic ambiguity and

the empirical strategies employed for management are explored. This case underscores the importance of a comprehensive and multidisciplinary approach to diagnosis and management in elderly patients presenting with febrile encephalopathy.

Febrile encephalopathy in the elderly is a multifaceted clinical entity that requires a high index of suspicion and a thorough diagnostic approach. The interplay of immunosenescence, atypical clinical presentations, and the presence of multiple comorbidities necessitates a tailored and patient-centric management strategy. Early recognition and prompt initiation of empirical therapy, guided by clinical judgment and available diagnostic tools, are crucial in improving outcomes in this vulnerable population.

Case Presentation

Patient Background

An 82-year-old male, with a known history of type 2 diabetes mellitus and suspected idiopathic parkinsonism, was admitted to the Medical Intensive Care Unit (MICU) of a tertiary care academic medical center in Northern India. He presented with progressive decline in mental status and persistent fever over several days. His family reported altered behavior, lethargy, and increasing confusion for three days prior to hospitalization, with no recent travel history or exposure to known infectious cases.
The patient had a background of chronic hypertension and impaired glycemic control. He was on regular anti-diabetic medication and antihypertensive therapy, with occasional compliance lapses. There was no history of seizures, trauma, or recent surgery. His vaccination status was up to date as per family report, and no significant exposure to tuberculosis or fungal spores was elicited during social history taking.

Initial Clinical Evaluation

Upon admission, the patient was febrile (102.6°F), with a fluctuating blood pressure peaking at 180/90 mmHg and a heart rate ranging from 108 to 126 beats per minute. Respiratory rate varied between 17–26 breaths/min, and oxygen saturation on room air fluctuated between 92% and 99%. He appeared visibly dehydrated with signs of electrolyte imbalance.

Neurologically, the patient was disoriented to time and place, with a Glasgow Coma Scale (GCS) score of 12 (E3V4M5). He did not exhibit neck stiffness, photophobia, or focal neurological deficits on initial examination. Fundoscopy was unremarkable, and no papilledema was observed. Motor and sensory responses were generally preserved.

Table 1: Laboratory Findings on Admission

Parameter	Result	Reference Range
White Blood Cell Count (WBC)	14,800/mm³	4,000–11,000/mm³
Neutrophil Count	Elevated	40–70% of WBCs
Erythrocyte Sedimentation Rate	Elevated	<20 mm/hr (male)
Serum Creatinine	Mildly Elevated	0.6–1.2 mg/dL
Blood Urea	Mildly Elevated	15–40 mg/dL
AST (SGOT)	Borderline Elevated	10–40 IU/L
ALT (SGPT)	Borderline Elevated	7–56 IU/L
Total Bilirubin	Normal	0.3–1.2 mg/dL
Electrolytes	Imbalanced	Na: 135–145 mmol/L; K: 3.5–5.0 mmol/L
Blood Glucose	Variable	70–110 mg/dL (fasting)

Table 2: Diagnostic Evaluation and CSF Analysis

Category	Findings/Notes
Provisional Diagnosis	Febrile encephalopathy in elderly diabetic patient
Differential Diagnoses	• CNS infections (viral, bacterial, TB, fungal) • Metabolic encephalopathy (uremic, hepatic, diabetic) • PRES • Pontine stroke • Neurodegenerative/ paraneoplastic syndromes
CSF Appearance	Clear and pale yellow
CSF Cytology	Paucicellular smears, degenerated inflammatory cells, no atypical/malignant cells
CSF Final Impression	Negative for malignancy
Fungal Microscopy (KOH)	Negative
CBNAAT + Line Probe Assay	Negative for Mycobacterium tuberculosis and drug resistance

Imaging Studies

A non-contrast Magnetic Resonance Imaging (MRI) brain scan with spectroscopy was performed.

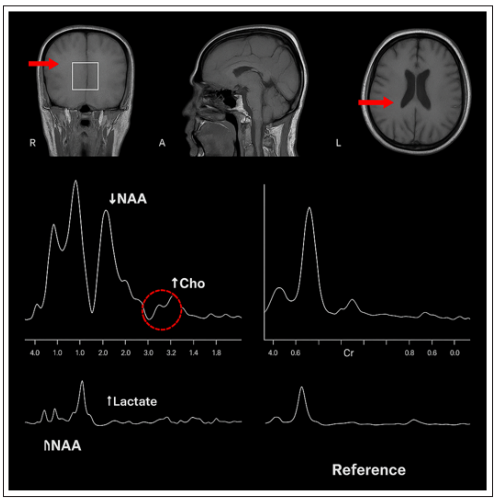

Figure 1: MR Spectroscopy and MRI Brain Imaging of Right Frontal Lobe Lesion

This figure demonstrates multimodal imaging including MR spectroscopy and corresponding MRI sections (coronal, sagittal, and axial) highlighting a lesion in the right frontal lobe (indicated by red arrows). The voxel for MR spectroscopy was placed over the lesion. Spectroscopic analysis reveals a reduced N-acetylaspartate (NAA) peak at approximately 2.02 ppm, indicative of neuronal loss or dysfunction. There is an elevated choline (Cho) peak around 3.2 ppm, suggesting increased cellular membrane turnover, commonly associated with neoplastic or demyelinating processes. A prominent lactate doublet peak near 1.3 ppm reflects anaerobic metabolism, which can be attributed to ischemia, necrosis, or mitochondrial dysfunction. Mildly decreased creatine (Cr) levels were noted. The calculated metabolite ratios were NAA/Cr = 1.37, Cho/Cr = 1.38, and Cho/NAA ≈ 1.00. These metabolic alterations are consistent with a non-specific encephalopathic process, potentially linked to systemic inflammation, metabolic derangement, or sepsis-related cerebral insult. Early-stage neoplastic or autoimmune etiologies are considered less likely based on the overall profile.

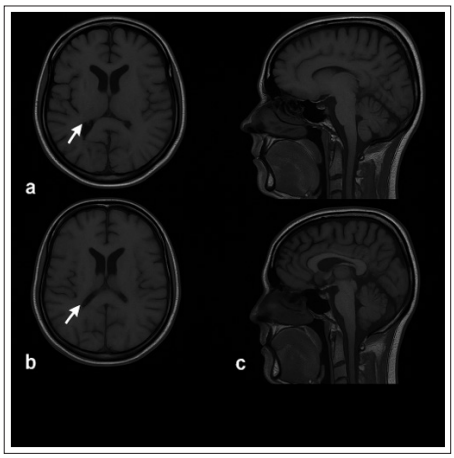

Figure 2: T2-Weighted MRI Brain Images Demonstrating Bilateral Parieto-Occipital Hyperintensities and Pontine Involvement

This figure presents a set of T2-weighted MRI brain images illustrating key findings of a multifocal encephalopathic process:

(a) Axial T2-weighted MRI shows symmetric hyperintensities in the bilateral parieto-occipital regions (marked by white arrows). These changes are characteristic of a diffuse encephalopathic process and suggest conditions such as Posterior Reversible Encephalopathy Syndrome (PRES) or toxic-metabolic encephalopathy. The absence of mass effect and surrounding edema supports a non-neoplastic etiology.

(b) Another axial T2-weighted slice further confirms bilateral parieto-occipital involvement with similar hyperintensities, reinforcing the symmetric and diffuse nature of the abnormal signal pattern.

(c) A sagittal T2-weighted image highlights a focal area of hyperintensity in the pons, consistent with an acute pontine infarct. This additional finding indicates a concurrent ischemic insult, pointing to a multifocal pathology that includes both potentially reversible encephalopathy and localized ischemia.

These images collectively support a diagnosis involving both diffuse and focal brain injury patterns, commonly seen in hypertensive crises, sepsis, or metabolic disturbances.

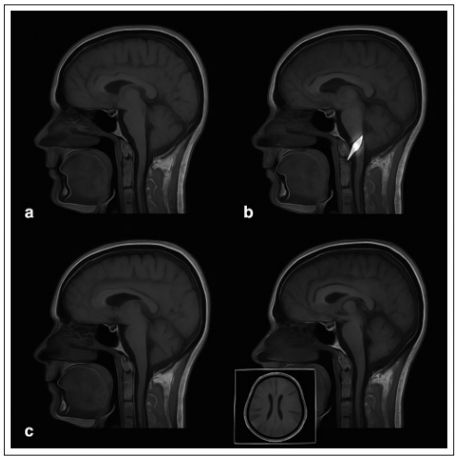

Figure 3: Multisequence Sagittal Brain MRI (Plain and Post-Contrast T1 Images)

Sagittal T1-weighted MRI images of the brain illustrating midline and parasagittal structures across both non-contrast and contrast-enhanced sequences. The imaging shows no space-occupying lesion or abnormal enhancement, but demonstrates a focal pontine hyperintensity indicative of an ischemic insult.

(a) Mid-sagittal T1-weighted plain image showing normal midline structures, including corpus callosum and brainstem.

(b) Parasagittal plain T1-weighted image showing a focal hyperintensity in the pontine region (yellow arrow), suggestive of an acute ischemic lesion.

(c) Corresponding post-contrast T1-weighted image showing no abnormal enhancement or mass effect, reinforcing a non-neoplastic, ischemic etiology.

https://youtu.be/UmawMxSc-tc?si=vxgdbAByOgZUEBIm

Video link

Clinical video demonstrating orofacial dyskinesia and involuntary facial movements

This clinical video captures an episode of involuntary orofacial movements in an elderly male patient being evaluated for febrile encephalopathy. The movements are spontaneous, irregular, and purposeless, primarily affecting the lips, chin, and perioral region. They occur without voluntary initiation and persist despite external distraction, suggesting a neurological origin rather than behavioral or psychogenic causes. There is no evident ocular involvement, and the eyes have been intentionally obscured in the video to maintain patient confidentiality.

These dyskinetic features may indicate basal ganglia dysfunction or could represent a side effect of dopaminergic therapy (e.g., Syndopa Plus). In this case, the patient's clinical background—including suspected idiopathic parkinsonism and metabolic abnormalities—suggests that the movements may be related to parkinsonism or an encephalopathy-associated extrapyramidal manifestation.

The video serves as a valuable clinical adjunct, supporting the diagnosis by correlating with imaging findings (MRI and MR spectroscopy) and helping exclude focal structural lesions or seizure activity. The presence of such movement abnormalities in the setting of encephalopathy raises the possibility of a diffuse or multifocal neurological insult, potentially related to sepsis, metabolic derangement, or early neurodegenerative processes.

Table 3: Treatment Summary

Category	Medication/ Intervention	Dosage/Frequency
Antimicrobials	Inj. Meropenem	1 g IV TDS
	Inj. Linezolid	600 mg IV BD
	Inj. Azithromycin	500 mg IV OD
	Inj. Fluconazole	200 mg IV OD
Supportive	IV Fluids (Normal Saline)	As per hydration status
	Sliding Scale Insulin	Variable dosing
	Calcium Gluconate IV	Electrolyte correction
	Pantoprazole	40 mg IV OD
	Duolin + Budecort Nebulization	As needed
	Eye & Skin Care	To prevent pressure sores
Neurological	Tab. Syndopa Plus	125 mg TDS
	Tab. Lacosamide	100 mg BD
	Tab. Benipil	80 mg BD

Clinical Progression

The patient's fever gradually subsided by the fourth day, but intermittent confusion persisted. Blood pressures remained labile. Repeat MRI after 6 days showed no progression of the pontine lesion. The absence of positive microbiological cultures, malignancy markers, or fungal elements remained puzzling. Hence, the final clinical diagnosis remained "non-specific febrile encephalopathy with pontine infarct", likely of metabolic or inflammatory origin.

He responded partially to dopaminergic therapy and regained partial orientation. The facial movements persisted but reduced in frequency. No seizure activity was noted. Repeat metabolic workup was within normal limits.

By day 12, he was stable enough to be transferred to a step-down unit.

- **Clinical Video Demonstrating Orofacial Dyskinesia and Involuntary Facial Movements**

Discussion

Febrile encephalopathy in elderly patients presents a significant diagnostic and therapeutic challenge due to atypical clinical presentations, age-related physiological changes, and the presence of multiple comorbidities. The case of an 82-year-old male with persistent high-grade fever, altered mental status, and fluctuating hypertension underscores the complexity of diagnosing and managing such conditions in geriatric populations [6].

Atypical Presentations in the Elderly

Elderly patients often present with atypical features of infection, including absence of fever or localized symptoms. These presentations are compounded by age-related changes in the immune system, a process referred to as immunosenescence, which diminishes both innate and adaptive immune responses [6]. This immune decline includes reduced production of naïve T and B cells and increased levels of pro-inflammatory cytokines, contributing to chronic low-grade inflammation, often termed "inflammaging" [6]. Comorbidities such as diabetes, cardiovascular disease, and neurodegeneration further obscure clinical symptoms, leading to delayed recognition and treatment.

Diagnostic Challenges

Diagnosing febrile encephalopathy in the elderly is often difficult due to nonspecific signs and overlapping features of infectious and non-infectious etiologies. In this case, extensive investigations such as cerebrospinal fluid (CSF) analysis, magnetic resonance imaging (MRI), and magnetic resonance spectroscopy (MRS) were used to exclude common causes like tuberculosis, fungal infections, and malignancies. MRI revealed T2-weighted hyperintensity in the right pontine region, consistent with an acute infarct. MRS findings of reduced N-acetylaspartate (NAA) and elevated choline suggested neuronal loss and membrane turnover, findings often associated with metabolic or infectious encephalopathy [7].

Management Strategies

Empirical antimicrobial therapy is frequently initiated in elderly patients with febrile encephalopathy due to the high risk of rapid deterioration and diagnostic uncertainty. Supportive care, including correction of metabolic abnormalities, insulin management, and neuroprotective strategies, are essential components of treatment [8]. In the present case, stabilization with supportive care despite the absence of a definitive etiology illustrates the importance of a multidisciplinary, empirical approach in geriatric febrile encephalopathy [9].

Importance of Clinical Observation

The presence of orofacial dyskinesia observed in the patient may suggest basal ganglia involvement or could represent a side effect of medications. Clinical signs such as these are essential in guiding neurological assessments. Studies have demonstrated that cognitive and psychomotor impairments, including such involuntary movements, are common in encephalopathic states and can assist in clinical differentiation [10].

Conclusion

Febrile encephalopathy in the elderly is a multifaceted condition requiring a high index of suspicion, thorough diagnostic evaluation, and prompt empirical treatment. The atypical presentations and overlapping symptoms with other age-related conditions necessitate a multidisciplinary approach involving neurologists, infectious disease specialists, and geriatricians. Future research should focus on developing standardized diagnostic protocols and exploring the utility of advanced neuroimaging techniques in this population. Limitations in this case include the absence of definitive microbiological findings and the challenges in pinpointing the exact etiology of the encephalopathy. Nonetheless, the patient's gradual improvement underscores the efficacy of comprehensive supportive care in managing such complex cases.

Additional Information

Disclosures

Human subjects: Consent for treatment and open access publication was obtained by participants in this study.

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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