CASE REPORT

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Antibody-Negative but Not Immune-Negative: Seronegative Autoimmune Encephalitis Presenting as NORSE

ABSTRACT

Parry–Romberg syndrome (PRS) is a rare acquired disorder characterized by progressive hemifacial atrophy involving skin, subcutaneous tissue, muscle, and bone. We report a 38-year-old woman presenting with long-standing right-sided facial asymmetry, enophthalmos, and underlying hypothyroidism. Clinical evaluation revealed classical features of PRS without neurological involvement. The condition is believed to have a multifactorial etiology, including autoimmune, neurogenic, and vascular mechanisms. Diagnosis is primarily clinical, supported by imaging when required. Management is multidisciplinary, with immunosuppressive therapy during the active phase and reconstructive procedures after disease stabilization. This case highlights the importance of recognizing PRS and its association with autoimmune disorders, facilitating early diagnosis and appropriate long-term management.

Key words: NORSE, Antiepileptic drugs, immunotherapy

INTRODUCTION

Status epilepticus is a neurological emergency associated with high morbidity and mortality, particularly when seizures become refractory to first-line antiseizure medications.[1]

The International League Against Epilepsy (ILAE)has defined refractory status epilepticus (RSE) as the persistence of seizures despite the administration of appropriate doses of an initial benzodiazepine and suitable second-line antiepileptic drugs (AEDs). New-onset refractory status epilepticus (NORSE) is defined as refractory status epilepticus occurring in patients without pre-existing epilepsy and without an immediately identifiable acute structural, metabolic, or toxic cause.[2] NORSE represents a heterogeneous clinical entity, with autoimmune and parainfectious etiologies increasingly recognized as major contributors.[3] Autoimmune encephalitis accounts for a substantial proportion of NORSE cases, even in patients who test negative for known neuronal antibodies.[4] Seronegative autoimmune encephalitis remains a clinical diagnosis based on characteristic presentation, neuroimaging findings, exclusion of infections, and response to immunotherapy.[5] Early initiation of immunomodulatory therapy has been shown to improve seizure control and neurological outcomes in NORSE patients.[6] We report a case of NORSE secondary to suspected seronegative autoimmune encephalitis in a young adult male who required prolonged intensive care management and multimodal immunotherapy.

CASE PRESENTATION

A 28-year-old previously healthy man presented with a 7 days history of low-grade fever and headache, followed by acute onset behavioral changes characterized by irritability and forgetfulness. Two days later, he developed an episode of impaired awareness associated with staring and unresponsiveness, which progressed to generalized tonic stiffening and postictal confusion.

He was initially evaluated at a peripheral hospital, where magnetic resonance imaging of the brain demonstrated bilateral symmetrical signal alteration appearing hyperintense on T2, FLAIR, DW images with corresponding ADC drop involving putamen and caudate nucleus features suggestive of encephalitis (Figure 1). Antiseizure therapy with levetiracetam was initiated; however, over the next 48 hours, the patient developed recurrent focal seizures manifesting as left hemifacial twitching and clonic jerks of the left upper limb, accompanied by progressive alteration in sensorium. Owing to persistent seizures and clinical deterioration, he was referred to our tertiary care centre for further management.

On admission, the patient was drowsy and irritable, not obeying verbal commands. Vital parameters were stable. Neurological examination revealed bilaterally equal and reactive pupils with preserved brainstem reflexes and no neurological deficit. Recurrent focal motor seizures involving the left face and upper limb were observed, consistent with focal status epilepticus.

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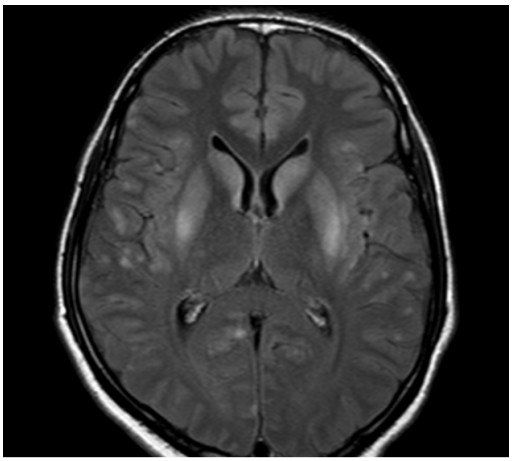

Figure 1: Symmetrical FLAIR Hyperintensities in bilateral Basal Ganglia(Putamen & Caudate)

Magnetic resonance imaging of the brain was repeated with contrast which revealed bilaterally symmetrical T2 hyperintensities in the basal ganglia and mesial temporal regions with diffusion restriction without post contrast enhancement, suggestive of encephalitis (Figure 2). Cerebrospinal fluid analysis showed mildly elevated opening pressure with normal glucose and protein levels and minimal pleocytosis. Extensive infectious evaluation including herpes simplex virus PCR, Japanese encephalitis virus PCR, and multiplex meningitis-encephalitis panel was negative. Autoimmune evaluation including cerebrospinal fluid NMDA receptor antibodies and serum autoimmune encephalitis antibody panel was also negative.

Continuous electroencephalographic monitoring demonstrated periodic bitemporal lateralized epileptiform discharges suggestive of ongoing epileptiform activity, which showed burst suppression pattern with anaesthetic infusion.

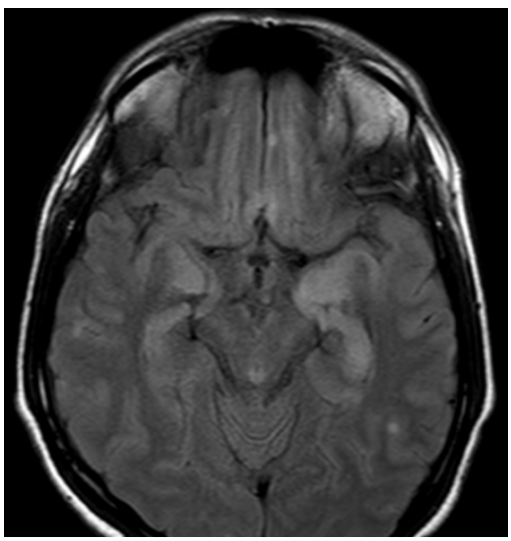

Figure 2: Symmetrical FLAIR Hyperintensities in Bilateral Medial Temporal Lobes

Despite escalation of antiseizure therapy with multiple agents including levetiracetam, lacosamide, valproate, fosphenytoin, topiramate, perampanel, the patient progressed to refractory status epilepticus. He required endotracheal intubation and initiation of continuous intravenous anaesthetic infusions with thiopentone and ketamine for seizure control. Multiple attempts at tapering anesthetic agents resulted in seizure recurrence, fulfilling criteria for super-refractory status epilepticus.

In view of the strong clinical suspicion of autoimmune encephalitis, empirical immunotherapy was initiated on day 5 of admission. The patient received intravenous intravenous immunoglobulin at a total dose of 2 g/kg administered over five days. Due to persistent seizure activity, a second cycle of intravenous immunoglobulin (2g/kg) was administered after 2weeks of the first cycle, followed by rituximab (500 mg) as second-line immunotherapy.

Following immunomodulatory treatment, the patient demonstrated gradual neurological improvement with progressive reduction in seizure frequency and improvement in sensorium. Repeat magnetic resonance imaging showed partial resolution of signal abnormalities in the basal ganglia and mesial temporal regions. He was subsequently weaned off anesthetic infusions and mechanical ventilation. Over the following weeks, the patient remained seizure-free on oral antiseizure medications and was discharged in stable neurological condition with preserved higher mental functions.

DISCUSSION

NORSE is a rare but devastating neurological condition, accounting for approximately 20% of refractory status epilepticus cases admitted to intensive care units[1]. Autoimmune encephalitis is now recognized as one of the leading identifiable causes of NORSE, particularly in young adults without prior epilepsy.[3] Up to 50% of autoimmune encephalitis associated NORSE cases remain antibody-negative despite extensive testing, highlighting the importance of clinical judgment.[4] MRI findings involving the mesial temporal lobes and basal ganglia, as observed in our patient, are commonly reported imaging patterns in autoimmune encephalitis and NORSE.[5]

EEG findings such as periodic lateralized epileptiform discharges and burst suppression patterns reflect severe cortical hyperexcitability and are associated with prolonged disease course.[7] Current expert consensus recommends early escalation to continuous intravenous anesthetic agents for seizure suppression in refractory and super-refractory status epilepticus.[8] Immunotherapy with corticosteroids, intravenous immunoglobulin, or plasmapheresis is recommended in suspected autoimmune NORSE, even before antibody results are available.[6] Second-line immunotherapy such as rituximab is advised in patients with persistent seizures or incomplete response to first-line immunomodulation.[9] Delayed initiation

of immunotherapy has been associated with poorer functional outcomes and prolonged ICU stay.[10] Most of the survivors eventually develop multidrug-resistant epilepsy on long-term follow-up and significant cognitive and functional impairment. Prolonged ICU stay, duration of barbiturate induced coma, and use of multiple anesthetic agents have been associated with greater risk of complications including cardiovascular (hypotension requiring the use of vasopressors, cardiac arrhythmias), gastrointestinal (liver dysfunction, ileus, gastric ulcers), infectious (pneumonia, urinary tract infection), hematological (anemia, thrombocytopenia, pulmonary embolism), electrolyte abnormalities (hypo or hypernatremia, hypophosphatemia, severe acidosis), and worse outcomes.[11] Our patient demonstrated gradual neurological improvement following combined immunotherapy, supporting an immune-mediated pathophysiology despite negative antibody testing. However, he continues to have focal seizures if antiseizure medication withdrawal is attempted. So, NORSE has evolved into a chronic epilepsy.

CONCLUSION

New-onset refractory status epilepticus represents a rare but life-threatening neurological emergency that requires prompt recognition and aggressive management. This case highlights the diagnostic and therapeutic challenges posed by seronegative autoimmune encephalitis presenting as NORSE, where the absence of identifiable neuronal antibodies should not delay initiation of immunomodulatory therapy. Our patient demonstrated significant clinical and radiological improvement following early escalation of antiseizure treatment combined with stepwise immunotherapy, including corticosteroids, intravenous immunoglobulin, and rituximab.

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