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Refractory status epilepticus secondary to Neurexin-3α encephalitis: A case report

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Abstract

New–onset refractory status epilepticus (NORSE) is a rare and challenging disease entity that is associated with high morbidity and mortality. Among the NORSE cases with a proven aetiology, autoimmune encephalitis has been identified as a leading cause. Here we describe a young man who presented with NORSE and was eventually found to have serum autoantibodies against Neurexin-3α, a synaptic molecule that has recently been implicated as a target in the pathogenesis of a novel form of autoimmune encephalitis. The patient's seizures responded to plasmapheresis, though the patient eventually died from sepsis. This case shows that Neurexin-3α encephalitis is a possible cause of NORSE, and plasmapheresis may be an effective treatment.

Keywords: Neurexin-3α, autoimmune encephalitis, NORSE, new-onset refractory status epilepticus

INTRODUCTION

New onset refractory status epilepticus (NORSE), is difficult to treat and often associated with poor outcomes.[1-3] In a series by Gaspard *et al*.[3], 52% was cryptogenic, 19% immune-mediated, 18% paraneoplastic and the rest was due to infection after extensive evaluation. We describe a case of a young man who presented with NORSE and eventually diagnosed with Neurexin-3α encephalitis.

CASE REPORT

A previously healthy 18-year-old man presented with acute confusion and first onset generalised tonic–clonic seizures, preceded by five days of fever and headache. On examination, he was febrile, tachycardic and drowsy with significant neck stiffness, raising the suspicion for acute meningoencephalitis. He had no focal neurological deficit. Systemic examination was unremarkable.

Investigations showed lymphopenia, mild thrombocytopenia and transaminitis. Kidney function test was normal and inflammatory markers were not elevated. Magnetic resonance imaging (MRI) of brain was normal. Cerebrospinal fluid (CSF) analysis showed pleocytosis (80 nucleated cells) with lymphocytic predominance (76% lymphocytes), raised protein (0.68 g/L) and normal glucose (3.7 mmol/L, 84% of serum glucose). He was treated for possible viral or partially treated bacterial meningoencephalitis with IV rocephine 2 g BD and IV acyclovir 500 mg 8 hourly. Another differential diagnosis was autoimmune meningoencephalitis and diagnostic tests were sent (Table 1). IV lorazepam and levetiracetam were initially started for treatment of status epilepticus.

The patient continued to have generalized tonic-clonic seizures and required intubation and intensive care. Continuous electroencephalogram (EEG) monitoring showed electrographic seizures originating from the left hemisphere, suggestive of focal epilepsy in the left hemisphere (Figure 1). IV phenytoin, valproic acid, phenobarbital, midazolam and ketamine were rapidly added on to achieve seizure control. Adjunctive antiepileptic drugs used included topiramate, gabapentin and perampanel. Despite these medications, the patient remained in a state of refractory status epilepticus.

Extensive serum and CSF investigations done in our institution (Table 1) were non-yielding in elucidating for a cause. Serum Glycine receptor, GABA-A receptor and Neurexin-3α autoantibodies were not available for testing at our hospital and sent to Neuroimmunology Centre in Oxford, United Kingdom for testing.

In view of the young age, abnormal CSF, normal neuroimaging, failure of identification of any specific microorganism and persistent seizures, autoimmune meningoencephalitis was strongly considered and plasma exchange (PLEX) was initiated on day three of admission. EEG showed significant burst suppression of seizure

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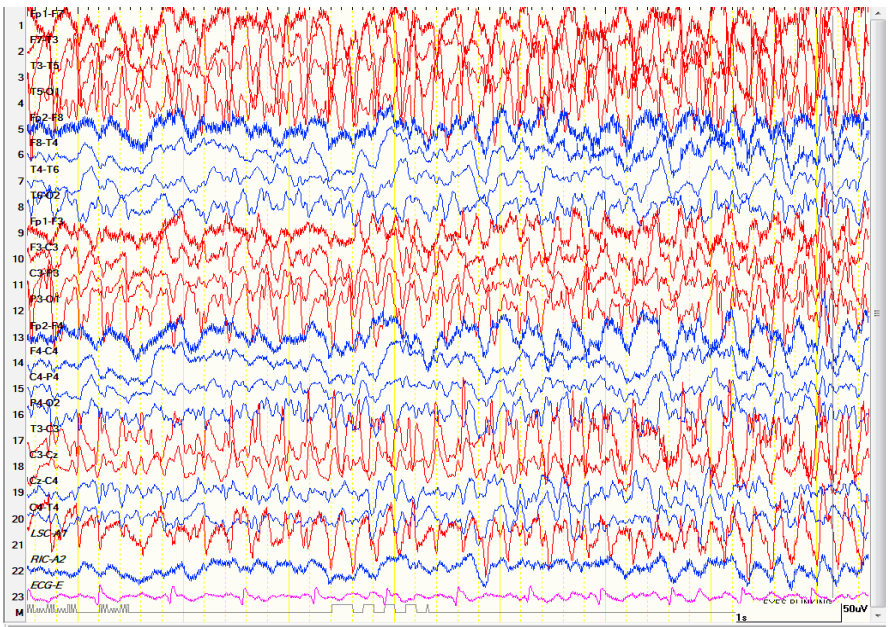

Figure 1. EEG (AP-bipolar montage) before initiation of plasma exchange showing electrographic seizure originating from left hemisphere

activity (Figure 2), together with abolition of clinical seizures, lasting 10.5 hours after the first cycle of PLEX, suggesting the disease mechanism is antibody-mediated. Second cycle of PLEX was followed by 1.5 hours of burst suppression together with cessation of clinical convulsions. Seizures recurred after this initial response and there was a plateau in clinical response to further plasma exchanges. He underwent six cycles of plasma exchange over two weeks. In view of improvement with PLEX, he was treated with a five-day course of IV methylprednisolone 1g daily followed by IV immunoglobulins 0.4g/kg/day for another five days.

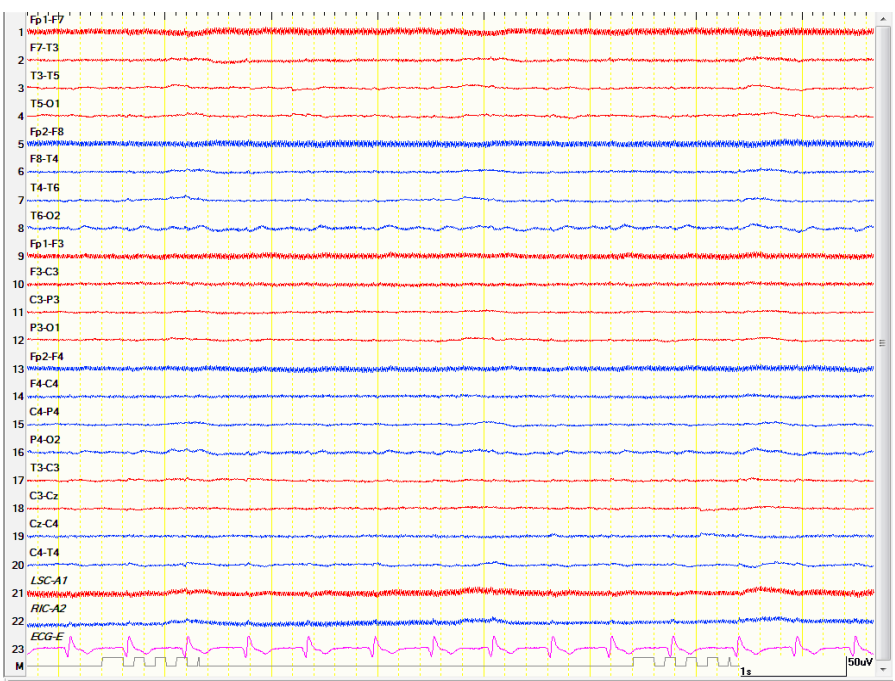

Figure 2. EEG (AP-bipolar montage) after 1 cycle of plasma exchange.

Table 1: Serum and CSF tests performed in local institution

Aetiology		Sample	Investigation
infection	bacterial/ mycobacterial	serum	aerobic and anaerobic bacterial culture
			syphilis VDRL
			mycoplasma antibody
			legionella antibody
			leptospira IgM antibody
			rickettsia IgM antibody
		CSF	gram stain
			aerobic and anaerobic bacterial culture
			syphilis VDRL
			AFB smear
			Mycobacterium tuberculosis (MTB) PCR
		sputum	AFB smear and culture
	viral	serum	dengue NS1 antigen
			zika PCR
			HIV antibody
			cytomegalovirus DNA
		CSF	cytomegalovirus, herpes simplex, herpes zoster, *Toxoplasma gondii* PCR
			herpes simplex PCR
			enterovirus PCR
		throat swab	enterovirus PCR
			influenza A/B/HN1
	fungal	serum	*Cryptococcus neoformans* antigen
		CSF	fungal microscopy
			india ink
autoimmune		serum, CSF	NMDA receptor, AMPA receptor, GABA-B receptor, LGl-1, CASPR2 autoantibodies
		serum	anti-nuclear antibody
			anti-double stranded DNA antibody
			anti-Ro/La antibodies
			anti-thyroperoxidase and anti-thyrotropin receptor antibodies
paraneoplastic		serum	anti-Ri, anti-Yo, anti-Hu, anti-Ma2, anti-GAD65, anti-amphiphysin, anti-CV2/CRMP5 antibodies
metabolic		serum	creatinine, urea, electrolytes
		urine	porphyrins/porphobilinogens
toxins–related		urine	toxicology screen (positive for opiate; history of use of paracetamol and codeine given by general practitioner clinic before admission)

(VDRL: veneral disease research laboratory, IgM: immunoglobulin M, AFB: acid-fast bacilli, NS1: non-structural protein 1, PCR: polymerase chain reaction, HIV: human immunodeficiency virus, DNA: deoxyribonucleic acid)

Unfortunately, he succumbed to multiple hospital-acquired infections, ileus and multi-organ failure. On day 19 of admission, seizures stopped and EEG showed minimal voltages suggestive of diffuse encephalopathy without electrographic seizure activity. MRI brain showed extensive cerebral edema consistent with hypoxic-ischemic encephalopathy. He was certified with brain death and extraordinary life support was withdrawn.

A week after our patient's demise, serum Neurexin-3α autoantibody test using cell-based assay returned positive, scoring 2.5 at a titre of 1:100.

DISCUSSION

Neurexin-3α is part of a family of synaptic cell–adhesion molecules that are instrumental in the formation and maturation of synapses[4]. Neurexin-3α encephalitis was first reported by Gresa-Arribas *et al*. in 2016.[5] The authors demonstrated alteration of neuronal synaptic formation by Neurexin-3α antibodies at a cellular level and also identified autoantibodies to Neurexin-3α in paired serum and CSF samples of five patients who presented with headache and fever followed by rapid neurological deterioration with encephalopathy and refractory seizures. Interestingly, we note striking similarities between our patient's presentation and patient two, the only male patient in Gresa-Arribas *et al*.'s study, who also had an aggressive disease course that was refractory to corticosteroids, and eventually culminated in coma, brain edema with tonsillar herniation, and a rapid progression to demise.

Our case report corroborates Gresa-Arribas *et al*.'s study in purporting a role for anti-Neurexin-3α antibodies in the pathogenesis of a novel form of autoimmune encephalitis whose full clinical spectrum remains uncertain. In our patient, this form of autoimmune encephalitis has manifested as NORSE with good albeit unsustained electrographic and clinical response to PLEX. Our case, alongside the other cases of Neurexin-3α encephalitis reported in the literature[5,6], illustrates the variable clinical presentations, propensity for an aggressive clinical course and variable immunotherapy responses. We highlight the importance of recognizing Neurexin-3α antibody as a potential causative agent and recommend antibody testing against Neurexin-3α antigen in patients presenting with NORSE as a positive result provides stronger basis to persist with more aggressive immunotherapies.

In the acute situation, the results of antibody testing may not be readily available as cell-based assays for these autoantibodies are not widely conducted, resulting in delay in diagnosis of autoimmune encephalitis and hesitation over initiation of aggressive immunotherapy which has been shown to improve outcomes.[7] We suggest clinicians initiate PLEX early after careful review for contraindications rather than late in the disease course, while awaiting evaluation for NORSE once initial microbiologic results have excluded an infectious cause. This is in light of the high morbidity and mortality that typically accompanies NORSE. PLEX removes the pathological antibodies and inflammatory cytokines causing disease, but the underlying disease process remains untreated. This explains the transient electrographic and clinical response in our patient. A response to PLEX is putative evidence for an antibody-mediated disease mechanism, viz autoimmune encephalitis. Together with PLEX, immunotherapy such as high dose pulsed methylprednisolone with its potential complications, should be started once there is evidence of antibody-mediated autoimmune disease. While the absence of response to PLEX does not definitively exclude an immune-mediated cause, response to plasma exchange is supportive of an antibody-mediated aetiology. Clinicians managing status epilepticus should keep in mind autoimmune encephalitis as an underlying aetiology in refractory status epilepticus.

DISCLOSURE

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Conflict of interest: None

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