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Case Report

'The great imitator': Neurosyphilis and new-onset refractory status epilepticus (NORSE) syndrome

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ABSTRACT

New-onset refractory status epilepticus (NORSE) is a syndrome of new-onset drug resistant status epilepticus that often has a catastrophic outcome. A 30-year-old man of Somali origin presented with refractory status to a district general hospital. A clinical diagnosis of NORSE syndrome was made, and he was transferred to the regional epilepsy center for immunomodulatory treatment and consideration for cyclophosphamide treatment. After transfer to the regional epilepsy center, his repeat cerebrospinal fluid tested strongly positive for syphilis, indicating a diagnosis of neurosyphilis, and the patient was treated with high-dose intravenous (IV) benzylpenicillin. His status epilepticus abated 24 h later.

New-onset refractory status epilepticus syndrome is a diagnosis of exclusion. Before instigation of potentially harmful neuromodulatory therapies, treatable causes such as neurosyphilis should be considered. We advocate the early transfer of refractory status patients to a specialist epilepsy center for both seizure management and cause determination.

1. Background

New-onset refractory status epilepticus (NORSE) is a syndromic diagnosis recognized by de novo status, without a history of epilepsy, in which no underlying structural, metabolic, or infective cause is identified. The syndrome can have very prolonged status epilepticus; it affects the young and healthy and frequently has a catastrophic outcome. Increasingly early aggressive intervention with immunomodulatory treatment such as steroids, including cyclophosphamide is advocated [1–4].

2. Case presentation

A 31-year-old Somali gentleman, with no prior history of epilepsy, presented with status epilepticus to his local district general hospital following a nonspecific prodrome of feeling generally unwell and weight loss for a few weeks. He was transferred to critical care, and initial treatment included phenytoin, ceftriaxone, and aciclovir. Over the course of 5 days, his condition did not respond to treatment with four antiepileptic drugs (AEDs). Additionally, the patient was sedated with midazolam, alfentanil, and propofol. Despite these measures, daily EEGs showed suboptimal control of seizure activity.

The patient's blood tests revealed a raised CRP, negative viral PCR (including hepatitis and HIV), negative blood cultures, and negative urine cultures. Initial lumbar puncture revealed a raised protein of 1.36 g/L, 0 polymorphs $\times 10^6$/L, 20 mononuclear cells $\times 10^6$/L, and a CSF glucose level less than half the serum glucose level (4.2/10.2), but no organisms were seen on the Gram stain. (See Table 1 in the Supplementary evidence for full tests.)

Head MRI showed a slightly increased signal in the anterior left temporal lobe on axial flair sequence. The patient was given empirical treatment for suspected new-onset refractory status epilepticus syndrome (NORSE) with 3 days of high-dose methylprednisolone and subsequently maintained on 60-mg prednisolone. The treating neurological team made a clinical diagnosis of new-onset refractory status epilepticus (NORSE) syndrome. On day 9 of his admission, he was transferred to the ITU department of the tertiary epilepsy center with the intention of giving plasma exchange and for consideration of cyclophosphamide treatment.

A further review at the specialist center revealed a previous diagnosis of treated genital syphilis 3 years ago. A repeat CSF examination was sent for treponemal serology; this came back as strongly positive in serum and CSF strongly indicating a diagnosis of neurosyphilis.

- Initial treponemal serology screen:
  - CSF RPR (rapid plasma reagin test) 1:4, TPPA (*Treponema pallidum* particle agglutination) 1:10,240,
  - serum VDRL (venereal disease reference laboratory) 1:4, serum TPPA 1:20,480.

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The patient was treated for 21 days on high-dose IV benzylpenicillin 2.4 g QDS for neurosyphilis in line with national guidelines. The patient's EEG demonstrated dramatic improvement in the next 24 h with no further electrographic or clinical seizures.

- Repeat syphilis screen 6 days later (posttreatment):
  - CSF RPR negative, TPPA negative,
  - serum RPR 1:2, TPPA 1:10, 240.

The repeat axial head MRI at 1 month demonstrated 'marked interval reduction in cerebral volume showing a central pattern of atrophy with enlargement of the lateral and third ventricles.'

Figs. 1 and 2 show the initial and repeat axial brain MRI scans at 1 month, respectively.

3. Outcome and follow-up

At 12-month follow-up, the patient remains with gross functional deficits and marked cognitive impairment and requires full nursing care including percutaneous endoscopic gastrostomy tube for feeding.

4. Discussion

New-onset refractory status epilepticus syndrome affects the young and is often associated with a poor neurological outcome [1]. Increasingly, it is considered to have an immune basis, and therefore aggressive immunomodulatory therapy is advocated at an early stage [2,3]. However, clinicians must remember that NORSE syndrome is a diagnosis made by excluding other causes, some of which such as neurosyphilis are readily treatable (see Table 2 in the Supplementary evidence for a list of known causes).

The incidence of seizures in neurosyphilis from studies is reported to range from 14 to 60%, but status epilepticus (SE) as the presenting symptom is very rare [5–7]. Furthermore, there are only a handful of cases of patients presenting with refractory status epilepticus secondary to neurosyphilis [6,7]. Neurosyphilis presents diversely and is known to have the ability to infect the nervous system at any stage of infection. The standard dose given for the treatment of syphilis is insufficient in treating neurosyphilis, and treatment is with high-dose benzylpenicillin [4,6–8].

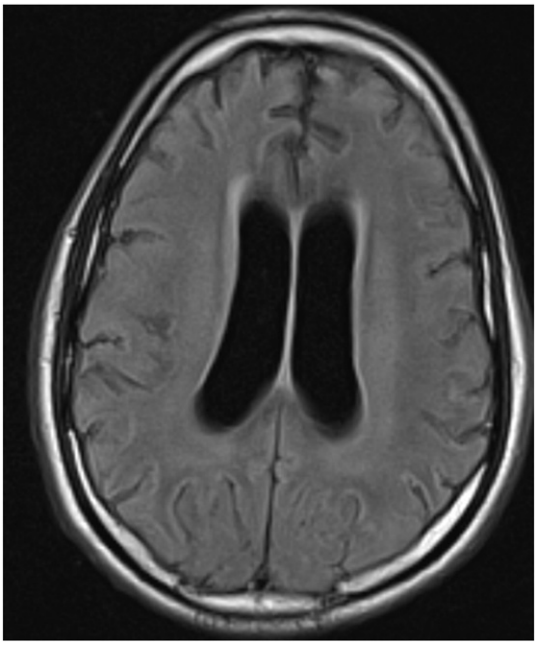

Fig. 1. Initial axial brain MRI scan at 1 month.

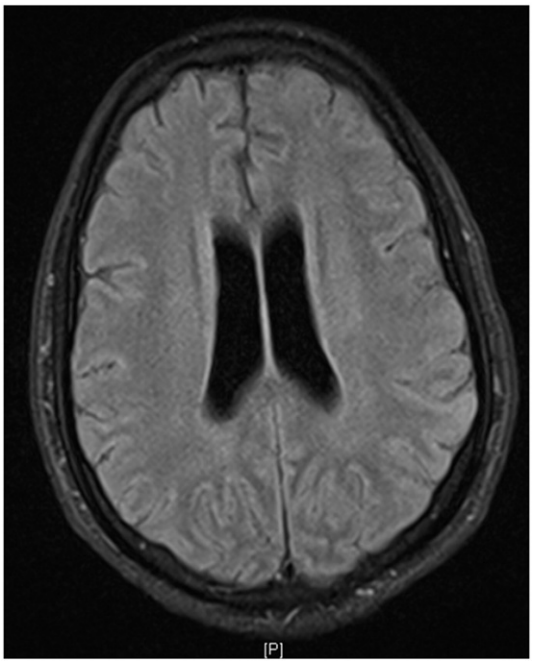

Fig. 2. Repeat axial brain MRI scan at 1 month.

While this case had the clinical characteristics of other cases of NORSE syndrome seen at our center, the history of 'treated' syphilis was a clue to the underlying cause. We would advocate that all patients with refractory status are tested for syphilis, allowing for early instigation of directed antibiotic therapy and avoidance of cytotoxic therapy. An etiological factor needs to be identified and be treated; this case emphasizes the need to perform an extensive workup as early as possible, and given the complexities of managing and determining the cause of status epilepticus, we suggest such patients should be transferred to a regional neuroscience center early in their illness.

5. Conclusion

New-onset refractory status epilepticus syndrome is a diagnosis of exclusion. Before instigation of potentially harmful neuromodulatory therapies, treatable causes such as neurosyphilis should be considered. We advocate early transfer of refractory status patients to a specialist epilepsy center experienced in rapidly managing refractory epilepsy for both seizure management and cause determination.

6. Learning points/conclusion

Any patient that is admitted with refractory epilepsy should have a full extensive search done to find a causative agent.

New-onset refractory status epilepticus syndrome is a diagnosis of exclusion and is increasingly treated with immunomodulatory therapies such as cyclophosphamide — always consider treatable causes such as neurosyphilis.

Neurosyphilis can present with status epilepticus.

Conflict of interest

We wish to confirm that there are no known conflicts of interest associated with this publication, and there has been no significant financial support for this work that could have influenced its outcome.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ebcr.2015.02.001.

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