Case Report
Volume 8:3, 2020
DOI: 10.37421/J Neurol Disord.2020.8.422

Journal of Neurological Disorders

ISSN: 2329-6895 **Open Access**

New-Onset Super-Refractory Status Epilepticus Following Fever: More than a Case of NORSE

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Abstract

We present the case of a healthy 32-year-old woman who came to our hospital due to fever and left otalgia. She subsequently developed dizziness and gait instability, opsoclonus-myoclonus syndrome, and altered level of consciousness. She was admitted to the intensive care unit, developing status epilepticus, which was refractory to third-line treatment with propofol and barbiturates. A thorough assessment including autoimmunity studies, viral testing, and mitochondrial disease testing yielded negative results. A brain magnetic resonance imaging scan revealed signal hyperintensities in both caudate nuclei and putamina, and gadolinium-enhancing small punctiform lesions in the left hemisphere and left cerebellar tonsil. Suspecting an immune-mediated disorder, we started treatment with high-dose steroids and plasmapheresis, in addition to different combinations of antiepileptic drugs. The patient was refractory to these treatments; electroconvulsive therapy improved the EEG tracing and may have helped manage status epilepticus. Subsequent examinations revealed paralysis of left cranial nerves IX, X, and XII, which resolved nearly completely in the final days of hospitalisation, leaving the patient practically asymptomatic. Our findings point to encephalitis with brainstem involvement and manifesting as cryptogenic new-onset refractory status epilepticus.

Keywords: Electroconvulsive therapy • Encephalitis • NORSE • Opsoclonus-myoclonus • Refractory status epilepticus.

Introduction

Status epilepticus (SE) is a common neurological emergency requiring early diagnosis and treatment [1]. In up to 40% of cases, SE is refractory to first- and second-line treatment [2,3]. Some of these refractory cases are healthy patients with no history of epilepsy or other relevant conditions.

This type of SE has recently been termed new-onset refractory status epilepticus (NORSE) and is generally associated with a poor prognosis [4]. However, favourable outcomes have been reported in some cases. The aetiology of NORSE often remains unknown; infectious, autoimmune, or genetic causes may be underdiagnosed [5].

There is no specific treatment for NORSE. Anecdotally, it has been suggested that immunomodulatory therapy may be effective in these patients, especially when administered early [6-8]. Such other treatments as hypothermia, the ketogenic diet, surgery, vagus nerve stimulation, and electroconvulsive therapy (ECT) have been used in some patients; however, there is insufficient evidence for conclusions to be drawn regarding their effectiveness and safety [9-13].

We present a case of NORSE with favourable outcome in the context of probable encephalitis associated with brainstem involvement and no identifiable cause.

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Received 13 May, 2019; **Accepted** 20 May, 2020; **Published** 27 May, 2020

Case Report

Our patient was a 32-year-old woman with a 5-day history of left otalgia and fever (39°C). She was diagnosed with otitis media and started antibiotic treatment with amoxicillin/clavulanic acid. Otalgia improved, but the patient returned to our hospital due to dizziness, nausea, and vomiting, and was admitted to the emergency department for further testing. On the same day she was admitted, she began to present gait instability and involuntary eye movements. The neurological examination revealed a fluctuating level of consciousness, opsoclonus-myoclonus, generalised hyperreflexia, and ataxic gait. An emergency head CT scan revealed no alterations and a CSF analysis yielded normal results. The patient was admitted to the intensive care unit (ICU) due to oxygen desaturation and increased drowsiness. Suspecting rhombencephalitis, we started antibiotic treatment with ceftriaxone, ampicillin, gentamicin, and corticosteroids.

Several hours after admission to the ICU, the patient presented simple focal motor seizures; according to the EEG, the irritative zone was located in the right frontocentral region. Focal motor seizures progressed to multifocal seizures associated with altered level of consciousness, that is, multifocal status epilepticus (Figures 1 and 2).

The patient received pharmacological treatment for SE, including valproic acid, levetiracetam and lacosamide, displaying no improvement; she was subsequently treated with phenytoin, clonazepam, and low-dose propofol infusion. Midazolam and ketamine were then added. Lack of response to treatment led us to administer thiopental. After good initial response, associated with a burst-suppression pattern, video-EEG revealed marked, diffuse involvement, associated with a discontinuous burst-suppression pattern and bilateral, independent signs of irritation. She also received high-dose intravenous methylprednisolone (1 g for 3 days), immunoglobulins (0.4 mg/kg/day for 5 days), and plasmapheresis (5 days). Due to lack of response, we decided to administer ECT. The patient received 2 sessions, each delivering 3 pulses at increasing doses (700 to 1000 mC). Additionally, 500 mg suxamethonium chloride and 400 mg caffeine were administered intravenously prior to the treatment to increase its effectiveness. ECT caused no seizures but was associated with marked improvements in EEG pattern.

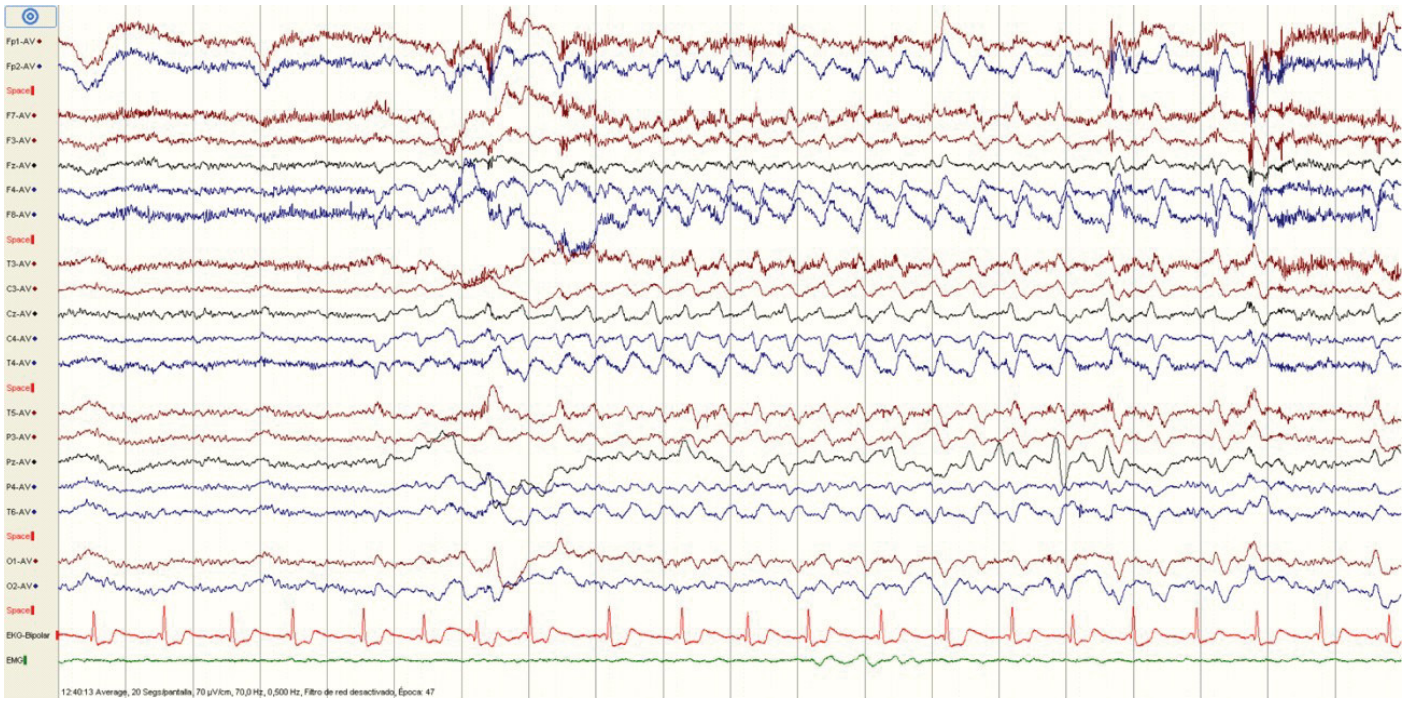

Figure 1. EEG of the first recorded seizure (transverse monopolar montage): focal motor seizures with epileptic recruiting rhythm in delta waves, predominantly in the right central area.

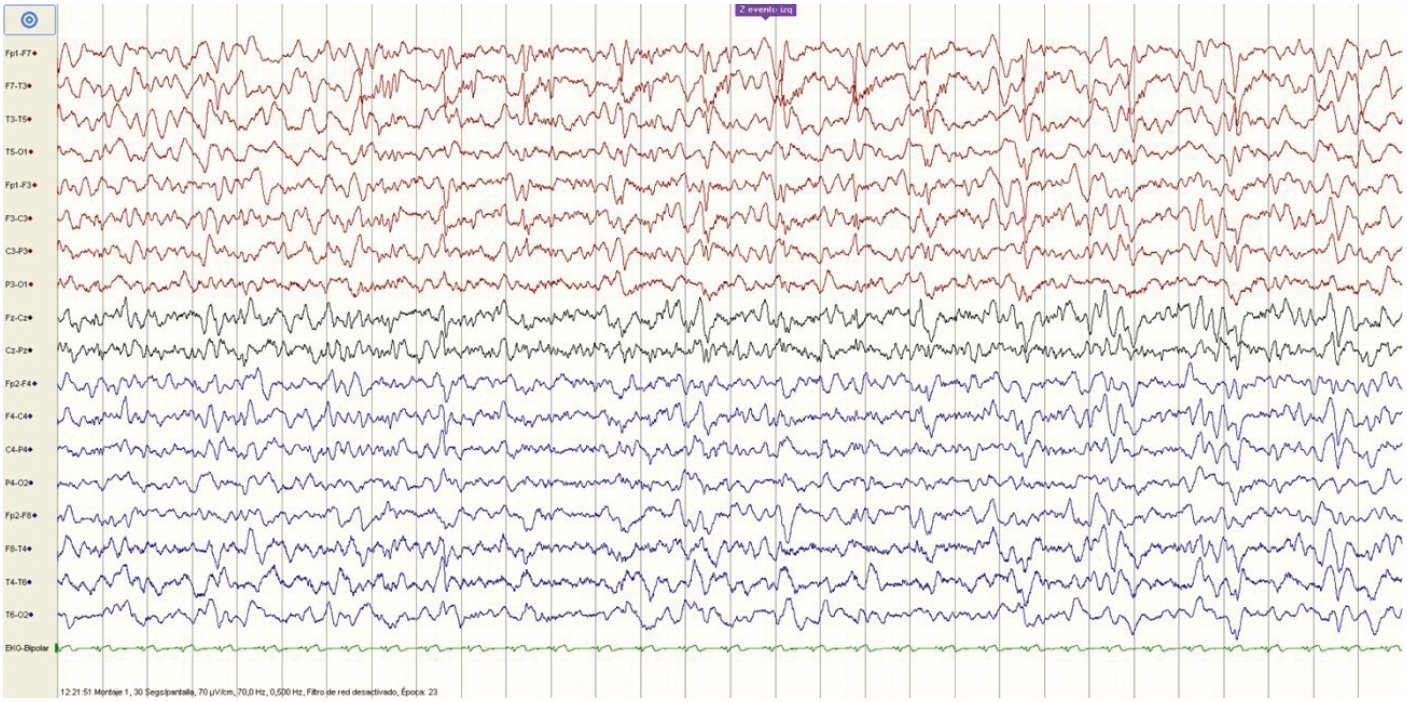

Figure 2. EEG of status epilepticus (longitudinal bipolar montage): generalized, multifocal epileptiform discharges; abnormalities were most frequent in frontotemporal regions (particularly on the right side). This pattern alternates with activity attenuations lasting 1- 2 seconds. This points to continuous multifocal epileptiform activity.

We subsequently prescribed the ketogenic diet, carbamazepine, and perampanel. Two days after the second session of ECT, and before propofol and midazolam were discontinued, the video-EEG ruled out status epilepticus, leading to the progressive discontinuation of antiepileptic drugs. Several days later, the patient once again presented SE; we resumed treatment with midazolam and ketamine, subsequently adding clobazam. Antiepileptic drug dosage was progressively reduced as the patient improved.

During the final days of the ICU stay, the patient displayed paralysis of the left cranial nerves IX, X, and XII, resulting in swallowing dysfunction; percutaneous endoscopic gastrostomy was therefore necessary. After one and a half months in the ICU, the patient was transferred to the neurology ward, where she experienced no complications. Complementary tests for different aetiologies of SE yielded no relevant results, as detailed below.

Laboratory analyses for autoimmune encephalitis yielded negative results. CSF and serum samples tested negative for the following antibodies: Hu, Yo, Ri, CV2, PNMA 2 (Ma2/Ta), amphiphysin, recoverin, Sox1, titin, Zic 4, Gad65, Tr (DNER), potassium channel antibodies, NMDA, AMPA1, AMPA2, GABA, CASPR2, and LGI1. A full-body CT scan revealed no abnormalities. CSF cytology yielded negative results for malignant cells. The patient also tested negative for oligoclonal bands. The most common causes of viral encephalitis (cytomegalovirus; herpes simplex virus types 1, 2, and 6; varicella-zoster virus; Epstein-Barr virus; enterovirus) were also ruled out; the results of a bacteriological study (including Listeria monocytogenes) also yielded negative results.

Results from complementary analyses for West Nile virus and Toscana virus were also negative. The results of the autoimmunity study (ANA, ds-DNA,

AMA, ASMA, cardiolipin IgG and IgM, TSH receptor) were normal except for initial positivity for thyroglobulin and microsomal antibodies; the patient subsequently tested negative for these antibodies.

The baseline brain MRI scan revealed bilateral, symmetrical hyperintensities of the caudate nuclei and putamina, as well as small, gadolinium-enhancing punctiform lesions in the left hemisphere and cerebellar tonsil; these were nonspecific and were barely visible on the follow-up MRI scan (Figures 3 and 4).

A biopsy of the vastus medialis and a study of the mitochondrial electron transport chain revealed no abnormalities. The results of the neurological examination upon discharge were normal except for mild dysphonia, weak gag reflex bilaterally, and mild left cranial nerve XII paralysis. At 6 months after discharge, the patient has experienced no further epileptic seizures and is independent in the activities of daily living; her only sequelae are mild short-term memory loss and difficulty concentrating.

Discussion

Our patient, a healthy young woman with no history of epilepsy, developed super- refractory SE following fever; we were unable to identify the cause. This entity is frequently identified as cryptogenic NORSE [14]. According to recent studies, there is mounting evidence that a large percentage of cases are autoimmune in origin, with inflammation triggered by an antibody. According to this autoimmune hypothesis, the levels of inflammatory mediators would increase, leading to neuronal hyperexcitability, a continuous state of seizures, and drug resistance [15-17].

Gaspard et al. [14] published a retrospective study of 130 patients with NORSE assessed at 13 centres between 1 January 2008 and 31 December 2013, and found that 67 cases (52%) were cryptogenic. The most common identified aetiologies were autoimmune encephalitis (19%) and paraneoplastic encephalitis (18%). Both causes may be underestimated due to variability in the diagnostic tests used. According to some authors, cryptogenic NORSE may be associated with undetected antibodies or viruses; less frequently, cryptogenic cases may be due to channelopathies unmasked by fever or chronic epilepsy with explosive onset [14,16].

Our patient tested negative for a wide range of antibodies. From a clinical viewpoint, cryptogenic NORSE is indistinguishable from autoimmune NORSE. Refractory SE is very rarely viral in origin when infection due to the most common viruses has been ruled out. However, we performed numerous viral tests, including tests for West Nile virus and Toscana virus. Brain MRI identified nonspecific signs of inflammation, which were practically undetectable at 2 months of follow-up.

Our patient displayed signs of brainstem involvement: opsoclonus-myoclonus syndrome, ataxia (which eventually resolved), and paralysis of lower cranial nerves; ours is the first case of NORSE with these characteristics to be reported in the literature.

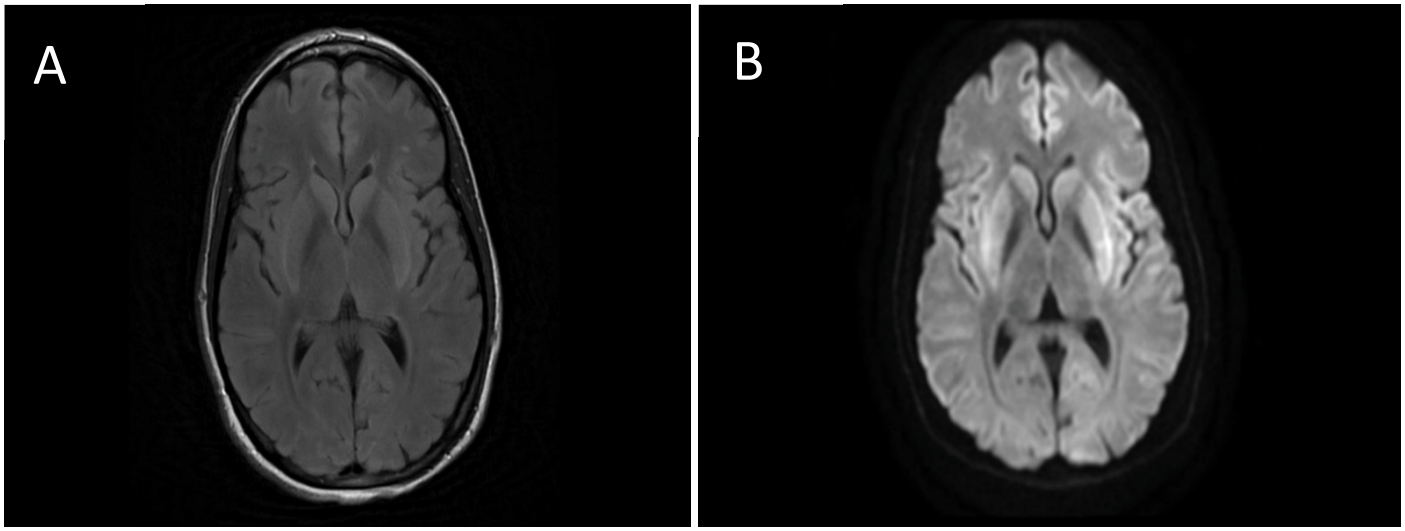

Figure 3. Brain MRI scan. A) Long TR sequences showing symmetrical, slightly hyperintense areas in both caudate nuclei and putamina. B) DWI revealed abnormal diffusion restriction in both putamina.

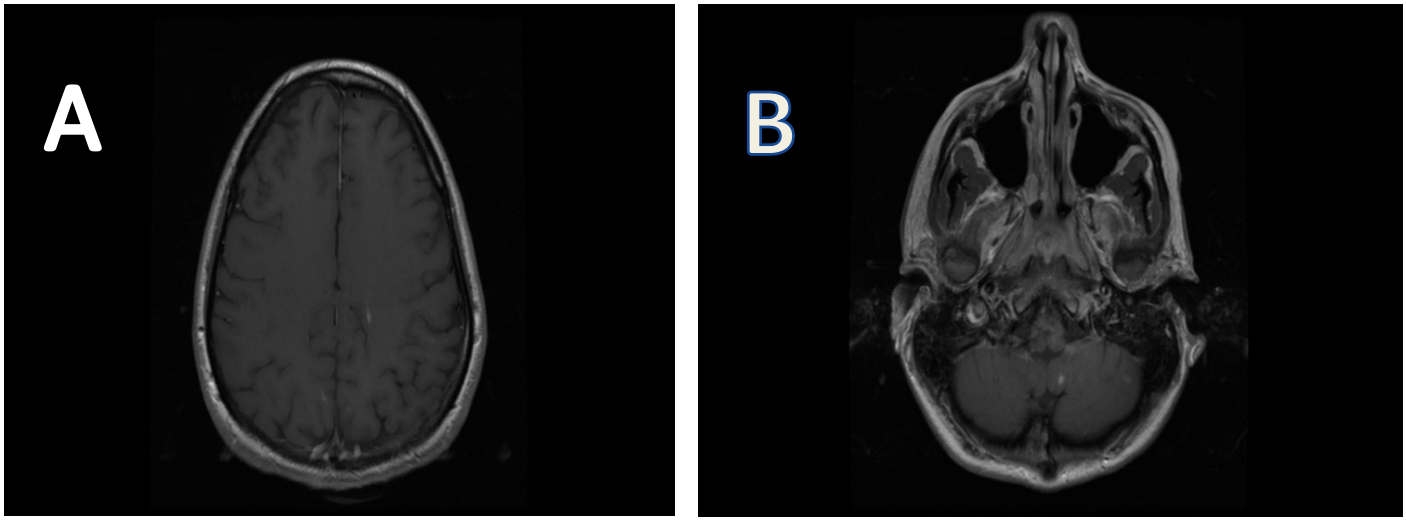

Figure 4. Follow-up brain MRI scan. A, B) The left hemisphere and cerebellar tonsil displayed small, nonspecific, gadolinium-enhancing punctiform lesions.

We hypothesise that our patient had encephalitis in the context of opsoclonus-myoclonus syndrome and lower cranial nerve involvement, which manifested as cryptogenic NORSE.

By definition, NORSE does not respond to first- and second-line treatment for SE and requires other alternatives, normally anaesthetics. The drugs most frequently administered for refractory SE are midazolam, propofol, and barbiturates (pentobarbital in the US and thiopental in Europe); midazolam has the best safety profile but is associated with a higher risk of recurring seizures. Barbiturates induce longer-lasting coma and therefore require mechanical ventilation, which increases the risk of respiratory complications. Propofol is associated with a small risk of potentially fatal propofol infusion syndrome, presenting with acidosis and kidney and heart failure [12,18-20].

Based on the hypothesis that NORSE is immune-mediated, we may be tempted to administer treatments to modulate the immune system. These include intravenous steroids, intravenous immunoglobulins, plasmapheresis, and certain monoclonal antibodies against inflammatory cells (eg, rituximab). The effectiveness of these treatments is based on small case series; controlled clinical trials are needed to recommend these treatments with a stronger level of evidence [6-8]. In our case, early immunotherapy with high-dose steroids, immunoglobulins, and plasmapheresis failed to improve the patient's symptoms, which led us to administer ECT.

ECT has been used to treat refractory SE in some cases of conventional therapy failure. The most widely accepted hypothesis supporting the use of ECT in SE is that it increases the levels of gamma-aminobutyric acid, inhibiting the propagation of epileptic discharges [21]. In a recent literature review on the use of ECT for refractory SE, Zeiler et al. [22] included a total of 19 patients (15 adults, 4 paediatric patients), 11 of whom responded to treatment (partial response in 4, complete resolution in 7). However, as patient samples were heterogeneous and stimulation time and parameters were highly variable, the authors concluded that there was insufficient evidence to recommend ECT for routine clinical practice (Oxford level of evidence 4, grade of recommendation D). The limited number of studies and the small size of the samples make it difficult to draw robust conclusions. However, it seems reasonable to use ECT for refractory SE as this technique is relatively safe compared to long-lasting coma induced by barbiturates, propofol, or ketamine [23]. In our case, we cannot confirm whether ECT contributed to resolution of SE or the favourable outcome; in any case, the EEG pattern visibly improved after treatment with the technique.

Furthermore, SE inevitably leads to multiple treatment changes and administration of a wide range of drug combinations; therefore, determining the treatment responsible for the resolution of SE or whether SE resolved spontaneously is extremely difficult.

Super-refractory SE has a mortality rate of 30% to 35%; at least 50% of survivors are left with long-term cognitive and functional impairment. Furthermore, most survivors develop chronic epilepsy, requiring life-long antiepileptic treatment. Only a small minority are able to return to normal life [24,25]. Most patients display brain atrophy after SE. However, a retrospective study conducted by Hocker et al. [26]. In 2016 found no correlation between brain atrophy and functional outcomes; brain atrophy should not, therefore, be considered a prognostic factor of functional recovery.

Conclusion

In conclusion, we were unable to determine the cause of NORSE, despite thorough testing. Increased awareness of NORSE may help determine the prevalence and aetiology of the condition and improve treatment. Early immunotherapy may help improve prognosis; further research is needed to determine the effectiveness of such other treatments as ECT. Ours is the first reported case of NORSE associated with signs of brainstem involvement. Our case shows that prognosis of NORSE is not necessarily poor; patients may achieve good long-term functional outcomes. This clinical case was presented in poster format at the 69th Annual Meeting of the Spanish Society of Neurology (2017).

Declaration of Interest

None.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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How to cite this article: Alicia Hernando-Asensio, María Asunción Martín-Santidrián, Ana Isabel Gómez-Menéndez and Beatriz García-López, et al. "New-Onset Super-Refractory Status Epilepticus Following Fever: More than a Case of NORSE." J Neurol Disord 8 (2020): 422 doi: 10.37421/jnd.2020.8.422