■ Clinical commentary

Epileptic Disord 2021; 23 (2): 403-406

Epileptic Disorders

Cryptogenic new-onset refractory status epilepticus (NORSE) following blood transfusion in a patient with severe anemia*

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Received July 3, 2020;
Accepted December 5, 2020

*The abstract alone was submitted to the 2020 American Academy of Neurology (AAN) meeting. The original intention was a poster presentation but this did not occur as the meeting was cancelled due to the COVID-19 pandemic.

ABSTRACT – New-onset refractory status epilepticus (NORSE) is a rare neurological emergency in which a patient without prior seizure disorder develops seemingly unprovoked status epilepticus refractory to treatment. We report the case of a middle-aged woman who developed NORSE after receiving multiple blood transfusions for subacute blood loss anemia secondary to menorrhagia. Although the mechanism is unclear, we propose that sudden changes in blood viscosity and vasogenic tone resulted in cortical edema and irritation. Although seizures have been documented in patients who undergo blood transfusion and develop posterior reversible encephalopathy syndrome (PRES), there was no radiographic evidence of PRES in this case. This is the first reported case of cryptogenic NORSE following blood transfusion.

Key words: epilepsy; refractory status epilepticus; NORSE; epileptic encephalopathy

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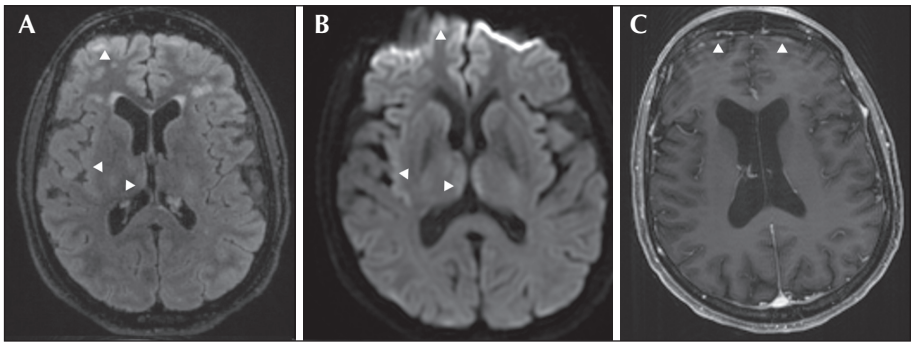
doi:10.1684/epd.2021.1267

Based on the current consensus definition, new-onset refractory status epilepticus (NORSE) is "a clinical presentation, not a specific diagnosis, in a patient without active epilepsy or other preexisting relevant neurological disorder, with new onset of refractory status epilepticus without a clear acute or active structurale, toxic or metabolic cause." [1]. Approximately 50% of NORSE cases have an eventual identifiable cause -inflammatory and autoimmune, infectious, genetic/congenital, and toxic, metabolic, or drug-related- with the other 50% remaining cryptogenic [2-3]. To our knowledge, none have previously been attributed to blood transfusion.

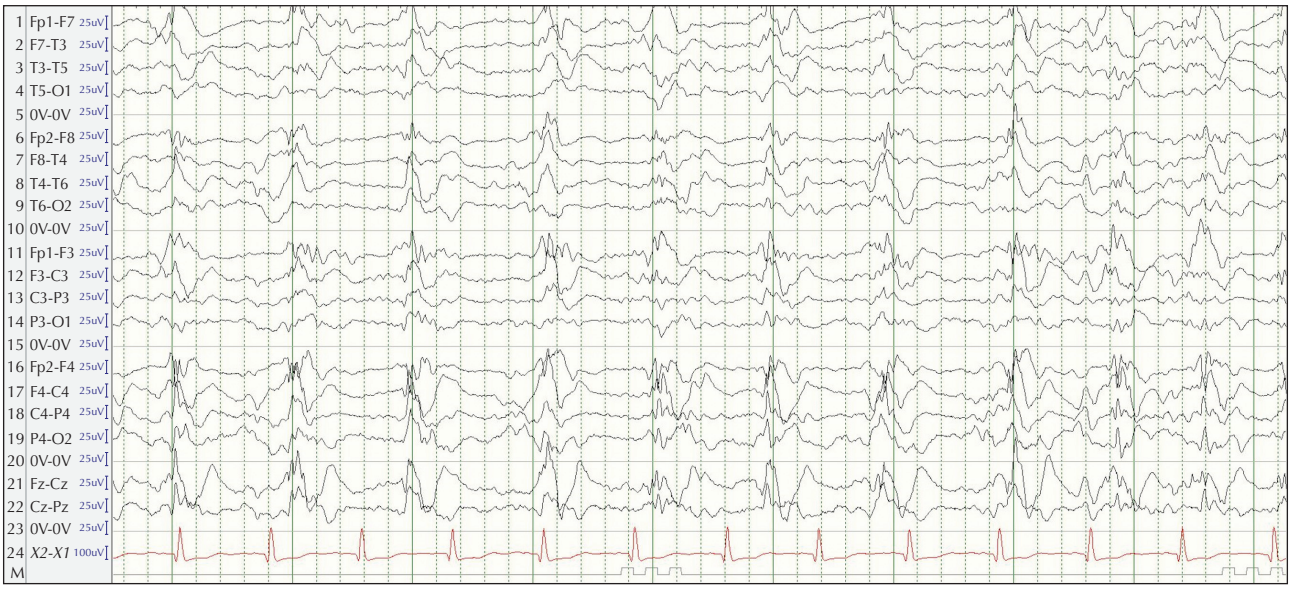
Case study

A 46-year-old woman with a remote history of thyroidectomy for papillary thyroid cancer presented with six months of intermittent menorrhagia, followed by one month of continuous menorrhagia and progressive fatigue. No other prodromal or neurological symptoms were evident. Initial laboratory workup revealed hemoglobin at 2.6 g/dL. After rapidly receiving three units of packed red blood cells, she became tachycardic and confused, with subsequent generalized tonic-clonic seizures that responded to lorazepam. She was then started on

levetiracetam. Serum calcium level after transfusion was 7.5 mg/dL. Lumbar puncture performed on the first hospital day showed mild neutrophilic pleocytosis (5-15 WBCs) without oligoclonal bands. She was started on empiric vancomycin, ceftriaxone, and acyclovir, but these were later discontinued after a CSF meningoencephalitis panel returned negative. Due to worsening encephalopathy, continuous EEG was performed and revealed frequent right frontal seizures. Subsequently, levetiracetam dose was increased and she was started on lacosamide. Brain MRI showed T2 hyperintense and diffusion-restricting lesions in the bilateral frontal and insular cortices and medial thalami (*figure 1A, B*). Additionally, the bifrontal lesions had subtle enhancement on post-contrast sequences (*figure 1C*). Brain MR angiography showed normal vasculature. She had no hypotension or cardiac arrest to suggest anoxic injury. On hospital Day 4, EEG showed 1-2-Hz right frontal polymorphic waves with superimposed fast rhythmic activity consistent with non-convulsive status epilepticus (*figure 2*). Despite escalation of anticonvulsant therapy to a combination



■ **Figure 1.** Initial MRI brain. (A) T2-FLAIR showing T2 hyperintensities (white arrow heads) in bilateral frontal and insular cortices and medial thalami. (B) Diffusion-weighted image showing diffusion-restricting lesions (white arrow heads) in the bilateral frontal and insular cortices and medial thalami. (C) Post-contrast T1 showing areas of bilateral frontal cortical enhancement (white arrow heads) corresponding to areas of frontal DWI/FLAIR abnormality.



■ **Figure 2.** EEG demonstrating non-convulsive status epilepticus. The settings for EEG are double banana montage, 10s epoch and sensitivity of 5 microvolts. The clip demonstrates non-convulsive status epilepticus characterized by polymorphic 1-2-Hz right frontal polymorphic waves with superimposed fast and rhythmic activity.

of levetiracetam, lacosamide, phenytoin, clobazam, propofol (70 mcg/kg/min) and midazolam (11 mg/h) infusions, she developed super-refractory status epilepticus, ultimately requiring pentobarbital infusion to achieve 80% burst suppression. Given that comprehensive infectious workup was negative, she received a five-day course of empiric high-dose intravenous methylprednisolone (1 g daily) for possible autoimmune encephalitis starting on hospital Day 5. By Day 11, her EEG improved dramatically and she was weaned off pentobarbital without further seizures. Intravenous immunoglobulin therapy and plasma exchange were considered but ultimately not pursued due to clinical improvement. Infectious workup was negative for a bacterial, viral, fungal, or prion process. Inflammatory and autoimmune workup including autoimmune encephalitis antibody panel was negative. Malignancy workup, including serum malignancy markers (CA-125, CA-19-9), endometrial biopsy, CT scan of chest, abdomen, pelvis, and PET imaging, revealed a uterine polyp without hyperplastic or carcinomatous features, but was otherwise unrevealing. Her anemia was attributed to this uterine polyp. She required a tracheostomy and gastrostomy tube. By Day 24, she started following simple axial commands. By Day 31, she was conversant with improving encephalopathy. She was discharged to an acute inpatient rehabilitation center and after another four weeks, she was nearly back to baseline though with slower processing speed.

Discussion

Neurological complications are rare following blood transfusion. Seizures after transfusion have been described in the context of citrate-induced hypocalcemia and PRES. While our patient had a history of mild hypocalcemia (7.3 mg/dL; thought to be due to parathyroid injury after prior thyroidectomy), her serum calcium levels remained stable after transfusion. Therefore, her seizures were unlikely to be related to citrate toxicity. There are also reports of posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS) following transfusion for chronic or subacute anemia. Of the published post-transfusion cases of PRES, most patients had anemia due to menorrhagia from uterine fibroids [4-8] with additional cases of aplastic and iron deficiency anemia [9]. Only two patients with menorrhagia developed status epilepticus requiring anesthetic agents and barbiturates [6-8]. In all cases, neurological deficits resolved within two weeks. No patients required tracheostomy, enteral feeding, or long-term inpatient rehabilitation. In one retrospective analysis of seven women who developed RCVS after blood transfusion, three developed non-refractory seizures five to seven days after transfusion [10].

All reported cases of transfusion-related PRES and RCVS occurred in the setting of subacute to chronic, but not acute anemia. The precise mechanisms of these entities remain speculative. One proposed mechanism involves compensatory cerebral vasodilation in response to chronic systemic hypoxia, such as in severe anemia [11]. With rapid transfusion, the rise in hematocrit and blood viscosity may induce sudden reversal of compensatory vasodilation [12] with resultant endothelial damage, vasogenic edema, and parenchymal irritation. Our patient's MRI lesions are suggestive of multifocal edema and do not show the posterior-predominant distribution typical of PRES. While we are not aware of any specific relationship between multifocal edema and NORSE, we suspect the underlying mechanism may be similar to PRES. A final alternate mechanism is paradoxical worsening of oxygen delivery related to blood transfusion secondary to packed RBC storage lesions [13], although the effects of this on the central nervous system have not been well described previously. While this ultimately remains a case of cryptogenic NORSE, there is a compelling argument for rapid blood transfusion as a provoking factor. The severe and unexpected outcome in our patient warrants more careful consideration of transfusion strategies in patients presenting with severe, chronic anemia. ■

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.
None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) A 28-year-old woman with a history of anxiety and benign uterine polyp (now excised) presents with new-onset seizures without return to baseline, meeting criteria for status epilepticus. The family also shares that she has been more anxious and paranoid in the past 2-3 days. She currently lives in the Bay Area, works as a veterinarian, and last month went on a road trip through Arizona and Utah. Infectious workup including blood culture, urine culture, chest X-ray, and CSF have been unrevealing. Brain MRI was without evidence of mesial temporal lobe sclerosis or other structural abnormality. Pelvis ultrasound was unrevealing. She ultimately requires three anti-epileptics, midazolam and propofol infusion to control her seizures. Which of the following workup would you next prioritize?

A. Serum IgG Cryptococcus sp., IgM/IgM Histoplasma, IgG Toxoplasma
B. Serum Lyme EIA with reflex to IgG, IgM
C. Whole-body PET
D. An extended toxicology screen to include lysergic acid diethylamide, phencyclidine

(2) A 35-year-old man with no known seizure risk factors presents after five generalized tonic-clonic seizures. He has another witnessed GTC seizure in the emergency department for which he receives lorazepam at 0.1mg/kg. He is loaded with levetiracetam at 60 mg/kg but has two additional seizures for which he receives a fosphenytoin load at 20 mg/kg. He continues to seize with no return to baseline and is subsequently intubated, started on midazolam infusion, and placed on continuous EEG monitoring. EEG reveals non-convulsive status epilepticus (NCSE). Despite increasing the rate of midazolam and addition of propofol infusion, he remains in NCSE requiring pentobarbital coma. By the 72-hour mark, he is now on four anti-epileptic agents and still requiring pentobarbital. The etiology of his seizures still remains unknown as extensive infectious, metabolic, toxic, neoplastic workup have been unremarkable. He has been treated empirically for an infectious encephalitis with vancomycin, ceftriaxone, acyclovir, and ampicillin. What should the next management consideration be?

A. Continue to watch and wait
B. A short course of high-dose steroids
C. IVIG
D. Cyclophosphamide
E. B or C both applicable

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".