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New-onset refractory status epilepticus after first dose of tozinameran

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Abstract

As the worldwide vaccination effort against COVID-19 gains traction, complications attributed to the vaccines are increasingly reported in medical literature. Herein, we describe the first two cases of new-onset refractory status epilepticus after receiving their first doses of tozinameran. These were attributed to underlying autoimmune responses against the vaccine given the temporal proximity to them receiving tozinameran, the absence of alternative diagnoses, the refractoriness of their seizures, and their clinical improvement only after administration of immunotherapies. Importantly, their cases supplement existing reports on the rare neurologic complications of the COVID-19 vaccines and encourage continued vigilance amongst the physicians amidst the pandemic.

Keywords: NORSE; COVID-19; vaccination; status epilepticus; encephalitis

INTRODUCTION

COVID-19 was identified in 2019 as a novel cause of severe acute respiratory distress syndrome and has been associated with neurologic complications involving both the central and peripheral nervous systems.[1] Declared a pandemic by the World Health Organization in March 2020, close collaboration between the pharmaceutical industry and government bodies saw the introduction of multiple vaccine platforms, ranging from mRNA-based to viral vectors.[1,2] As the global vaccination efforts intensify, reports on neurologic complications after vaccinations are increasingly reported in literature, although a causal relationship remains unclear.[2] Herein, we describe the two rare cases of new-onset refractory status epilepticus (NORSE) beginning five and eight days after receiving tozinameran (Pfizer-BioNTech) respectively.

CASE REPORT

Patient 1

A 28-year-old female presented with generalized tonic-clonic seizures (GTCS) after receiving tozinameran. She was without pre-existing medical disorders or drug allergies. She had just received her first dose of tozinameran eight days ago. She was afebrile, but was photophobic and lethargic, scoring 10 on the Glasgow Coma Scale (GCS; E3V2M5). Kernig sign was absent. Suspecting acute meningoencephalitis, intravenous (IV) antimicrobials were started together with IV levetiracetam for her seizures. Blood inflammatory markers, microbiologic cultures and assays, toxicology, and tests for metabolic, thyroidal, and electrolyte derangements, all returned normal. Lumbar puncture (LP) revealed a normal opening pressure (10cmH_2O). Cerebrospinal fluid (CSF) analysis however demonstrated elevated white cell counts (WCC; 8/uL) and protein levels (0.43g/L). CSF microbiologic assays and cultures were negative. SARS-CoV2 polymerase chain reaction (PCR) tests of nasopharyngeal swabs performed two days apart were negative. Brain magnetic resonance imaging (MRI) revealed bilaterally swollen medial temporal lobes which were hyperintense on T2 and fluid-attenuated (FLAIR) sequences (Figure 1A). Post-contrast T1 sequences demonstrated no abnormal enhancement.

Despite initial treatment measures, she developed myoclonic status epilepticus and required induction of barbiturate coma at the intensive care unit (ICU). Electroencephalography (EEG) demonstrated near-continuous seizures over both hemispheres (Figure 2, with description

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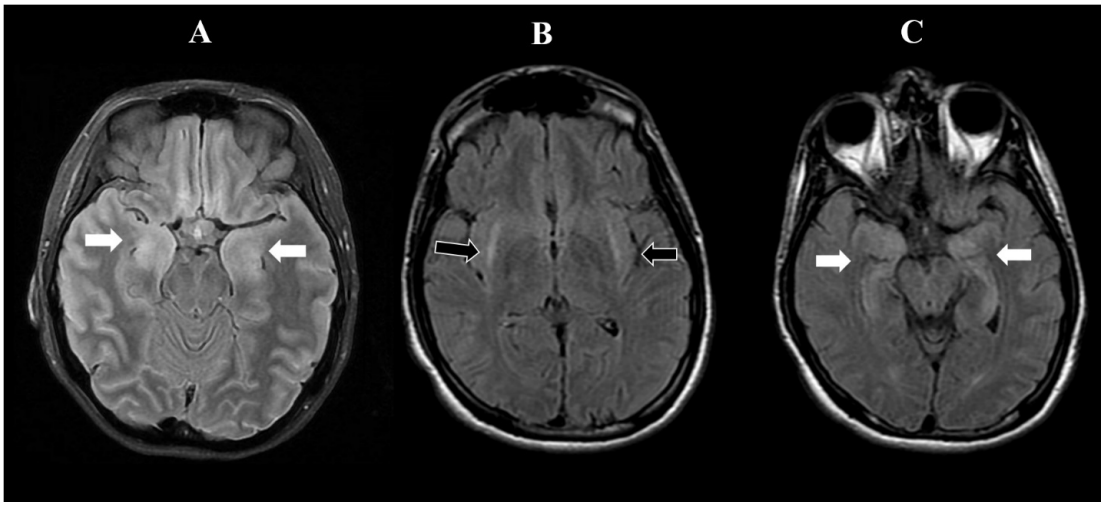

Figure 1. Brain MRI images of Patients 1 and 2. A: FLAIR sequence, axial projection of Patient 1's MRI, in which both medial temporal lobes (white arrows) appear hyperintense. B&C: T2 sequence, axial projection of Patient 2's MRI, in which bilateral claustra (black arrows) and medial temporal lobes (white arrows) were hyperintense.

of EEG features) despite her receiving enteral and intravenous anti-epileptic and anaesthetic agents (Table 1). The dosages of the aforementioned medications and their corresponding serum levels are described in Table 1. CSF and serum indirect immunofluorescence (IIF) were negative for antibodies against NMDAR, LGI1, CASPR2, AMPAR1/2, GABAb, and DPPX antibodies. Serum IIF tested negative for onconeural antibodies against Hu, Ri, Yo, CV2/CRMP5, and PNMa2/Ta. Serological tests for systemic autoimmune diseases were unremarkable.

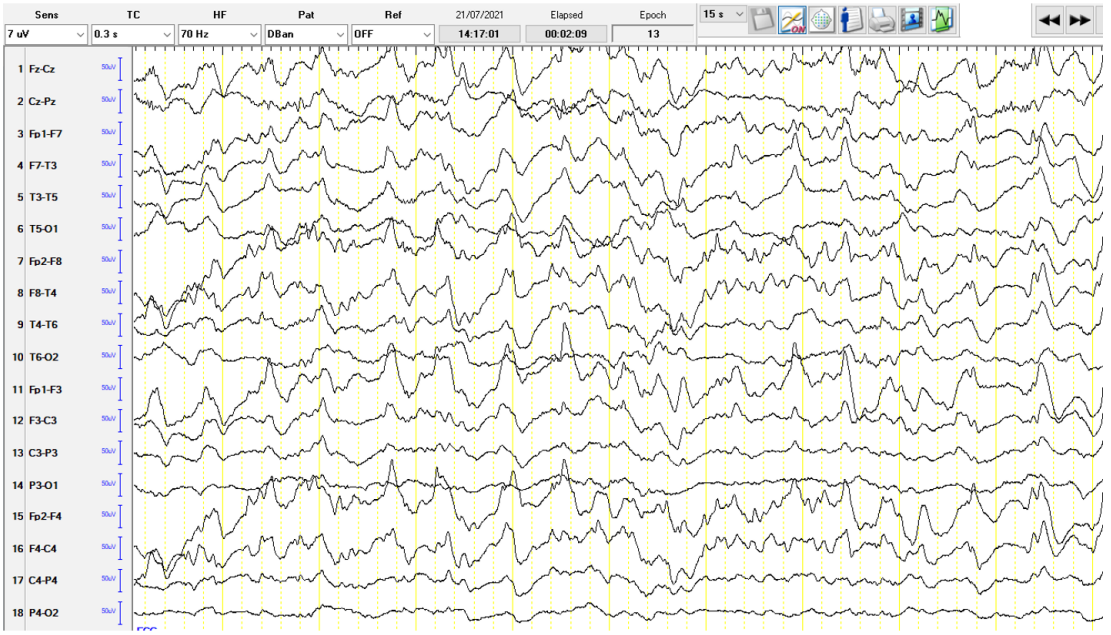

Figure 2. Representative 10-second epoch (double-banana bipolar montage; sensitivity: 7uV/mm; time base: 15 seconds) of Patient 1's extended EEG study (2.5 hours), showing EEG seizures over bilateral hemispheres maximally over both frontotemporal regions consisting of 10-12 Hz sharp waves mixed with 2-3 Hz activity and 1 Hz generalized periodic epileptiform discharges, occurring near-continuously throughout the entire recording, during which rhythmic twitches of the bilateral face and upper limbs were observed.

Table 1: Dosages of antiepileptic drugs

Pt	AEDs and their dosages during barbiturate coma	Serum levels during barbiturate coma	AEDs and their dosages at the time of writing
Pt 1	IV phenobarbital sodium 90mg BD	27.6 – 39.7mg/L	Discontinued
	IV propofol infusion 70-80mg/h	N/A	Discontinued
	IV phenytoin 100mg TDS	11.8 – 21.1mg/L	Discontinued
	IV midazolam infusion 5mg/h	N/A	Discontinued
	IV sodium valproate 800mg Q8H	57.2 – 67.8mg/L	PO 600mg BD
	IV levetiracetam 1g Q6H	N/A	PO 1g Q6H
	IV lacosamide 200mg Q8H	N/A	PO 200mg Q8H
	PO perampanel 12mg OM	N/A	PO 12mg OM
Pt 2	IV phenobarbital sodium 200mg TDS	N/A	Discontinued
	IV propofol infusion 80mg/h	N/A	Discontinued
	IV sodium valproate 400mg TDS	60.22mg/L	PO 1.2g TDS
	PO perampanel 12mg OM	N/A	PO 12mg OM
	PO topiramate 200mg BD	N/A	PO 75mg BD
	IV levetiracetam 1.5mg BD	N/A	Discontinued
	N/A	N/A	PO carbamazepine 400mg BD
	N/A	N/A	PO clonazepam 0.5mg ON/PRN

Abbreviations: AED, anti-epileptic drugs; IV, intravenous; PO, per-os; BD, twice a day; TDS, thrice a day; Q8H, 8-hourly; Q6H, 6-hourly; ON, at night; PRN, as required.

Computed tomography of her thorax, abdomen, and pelvis, plus a pelvic ultrasound, failed to demonstrate neoplasms.

She was diagnosed with NORSE in view of her refractory seizures, inflammatory CSF profile, and the negative microbiologic tests on both CSF and blood. Given NORSE's predilection for autoimmune aetiologies, she received IV pulses of methylprednisolone (1g/day for three days) and seven cycles of plasmapheresis. Ten months into her hospitalization, she displayed clinical improvement (best GCS: E3VtM5) on tailing doses of oral prednisolone but continued to be treated at the ICU, requiring multiple AEDs (Table 1) to remain free of seizures. Her most recent EEG at the time of writing demonstrated no seizures, showing continuous non-rhythmic generalized slowing of 3-6 Hz instead, consistent with the presence of severe diffuse encephalopathy.

Patient 2

An 18-year-old male presented with GTCs five days after receiving a booster dose of Tozinameran. He had no preceding medical history or drug allergies, and received his second dose of CoronaVac uneventfully 5 months before. This was his first exposure to tozinameran, after which he became febrile the day after. At presentation, he remained febrile (39.3°C) with a low GCS of 7 (E1V1M5). Kernig sign was absent. Two PCR tests of nasopharyngeal swabs were negative for COVID-19. Suspecting acute meningoencephalitis with accompanying seizures, he was treated with IV antimicrobials and levetiracetam. Laboratory investigations showed elevated WCC ($11.3x10^9$/L) and C-reactive protein levels (17.22 mg/L). Initial MRI with gadolinium and MR venography of the brain yielded unremarkable results. LP performed showed a normal opening pressure. CSF analysis revealed a mildly-raised WCC (5/uL) but with normal protein and glucose levels. CSF microbiologic assays and cultures were negative.

He developed status epilepticus (focal onset evolving into bilateral convulsive status epilepticus) despite initial treatment measures on the fourth day of hospitalization, refractory to high doses of anti-epileptic drugs (AEDs) as shown in Table 1. He was intubated and transferred to the ICU for the infusion of propofol (80mg/h) and the induction of barbiturate coma (Table 1). EEG showed semi-rhythmic slowing

of delta frequency with superimposed bursts of rhythmic beta activity, similar to the 'extreme delta brush' whilst on propofol infusion, but his seizures recurred when propofol infusion was stopped (Figure 3A and 3B respectively, with description of EEG features). Ketogenic diet with a fat to carbohydrate and protein ratio of up to 3:1 was started, although his blood ketones failed to achieve the target of more than 2.4mmol/L.

Due to the persistence of his electrographic seizures, an MRI brain with gadolinium was repeated on the tenth day of hospitalization, which showed hyperintense T2/FLAIR signals over bilateral claustra and medial temporal lobes (Figures 1B and 1C). CSF IIF was negative for antibodies against NMDAR, LGI1, CASPR2, AMPAR1/2, GABA-b, and anti-DPPX. CT of his thorax, abdomen, and pelvis yielded unremarkable findings. Diagnosed with febrile infection-related epilepsy syndrome (FIRES; a subset of NORSE)

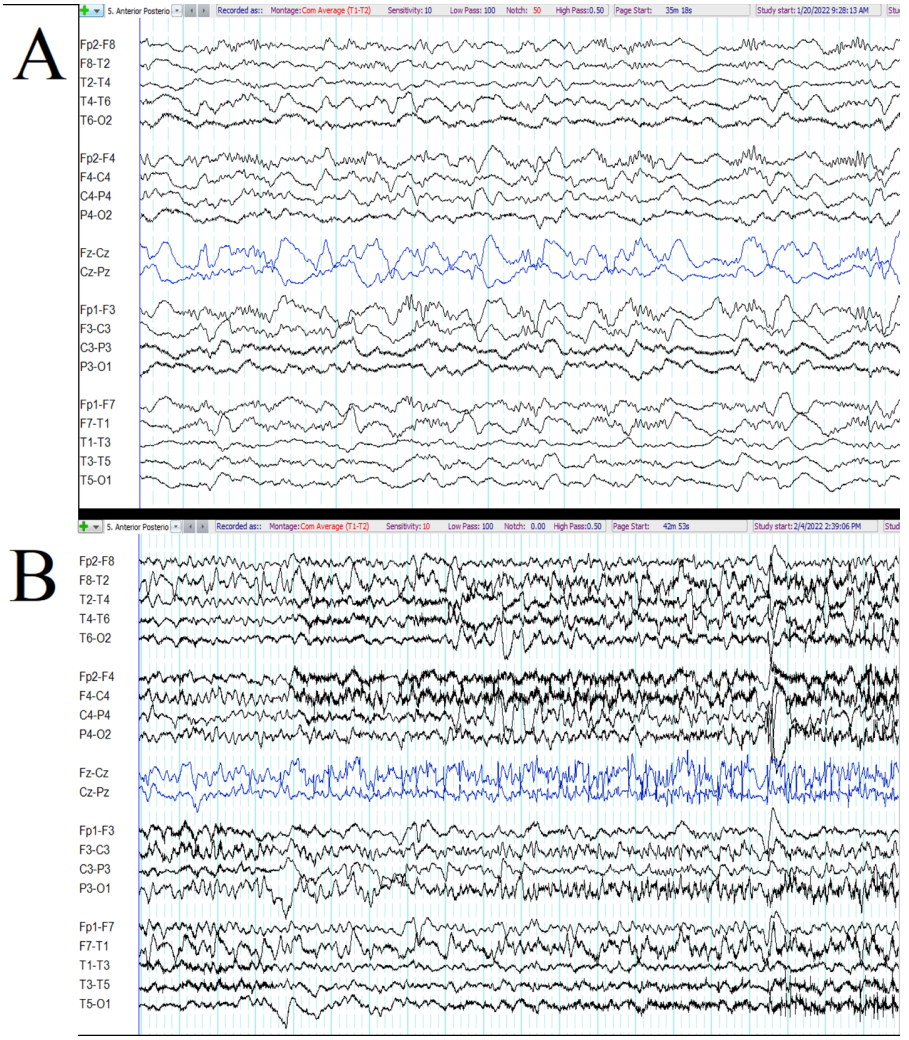

Figure 3. A: Representative 10-second epoch (antero-posterior bipolar montage, sensitivity: 10uV/mm; time base: 10 seconds) of Patient 2's EEG, showing semi-rhythmic slowing of delta frequency, with superimposed beta activity most prominently over the both fronto-central regions, reminiscent of the 'extreme delta brush' pattern. B: Representative 20-second epoch (antero-posterior bipolar montage, sensitivity: 15uV/mm; time base: 20 seconds) of Patient 2's EEG, showing the main findings of theta activity (4-6Hz) over the central region (Cz, Pz) in the first two seconds, which subsequently evolved to spike activities with accompanying tonic movement of the right leg and head deviation to the right, before generalized tonic-clonic movements were observed in all four limbs. The generalization of the clinical seizures was temporally correlated by the spread of spike activity on the EEG from the central regions to both hemispheres, lasting a total of 90 seconds before its abrupt cessation.

given his clinical and radiologic features and the ancillary test results, he was treated with a five-day course of IV methylprednisolone (1g/day), followed by five days of IVIg (0.4g/kg/day) but demonstrated no betterment of seizure control a week after the last dose of IVIg. IV tocilizumab was thus started then, with consequent improvement of the control of his seizures (Figure. 1C), allowing propofol infusion to be tapered off 17 days later, and he was discharged after 10 weeks of hospitalization. He displayed no sensorimotor deficits when reviewed two weeks later, and remained fully independent in his activities of daily living. He did, however, complain of difficulties with short-term memory, continued to experience infrequent brief GTCs lasting around 10 seconds twice a week, and remained in need of multiple oral AEDs (Table 1).

DISCUSSION

NORSE describes the rare clinical presentation of new-onset refractory status epilepticus in patients without pre-existing epilepsy or other relevant neurologic diseases, and without a clear acute or active structural, toxic, or metabolic cause.[4] It displays a predilection for children and young adults. A precipitating cause is identified in up to half of the adults, amongst which inflammatory aetiologies such as autoimmune encephalitides (sporadic or paraneoplastic) predominate.[5] With strong potential for the development of super-refractory status epilepticus, patients often require prolonged ICU stay and anaesthetic use, and with it the risk of further complications and poor clinical outcomes.[4]

To the best of our knowledge, these are the first two reported cases of NORSE from autoimmune encephalitis after receiving tozinameran, an mRNA-based vaccine by Pfizer-BioNTech. Antigenic cross-reactivity between SARS-CoV2 and human tissue has been discussed in preceding literature, and similar processes involving molecular-mimicry in vaccines have been proposed.[6-8] Reports of COVID-19 patients with autoimmune encephalitis and NORSE lend further support to the plausibility of an immune-mediated response due to molecular-mimicry by a still-unknown 'culprit' epitope within the spike protein, the latter awaiting future elucidation.[9-12] Coincidentally, Liu *et al*., described two elderly patients who developed encephalopathy and non-convulsive status epilepticus, seven days after receiving their first doses of elasomeran, an mRNA-based vaccine similar to tozinameran.[13] They reasoned that the vigorous inflammatory cascade induced by the production of SARS-CoV2 spike proteins within the central nervous system, coupled with reduced levels of brain-derived neurotropic factor (BDNF), provide the plausible mechanisms behind their seizures.[13,14] Binding of spike-proteins to angiotensin-converting enzyme 2 (ACE2) decreases BDNF levels and reduces the latter's ability to attenuate microglial activation.[15] Both mechanisms likely co-exist, explaining the refractoriness of our patient's seizures despite multiple antiepileptic and anaesthetic medications.

In conclusion, at the time of writing, these are the few, if not the first two reported cases of NORSE after the first dose of tozinameran. Although we can neither exclude the possibility of our patients' NORSE occurring entirely by chance nor its possible association with tozinameran (Naranjo Scale score of 3 for both), their temporal proximity in previously healthy adults and the absence of alternative diagnoses render a possible association difficult to ignore.[16] Their brain MRI findings, CSF profiles, their poor response to antimicrobials, the seizures' refractoriness to multiple AEDs and anaesthetic agents, and the remarkable resolution of their seizures after the administration of immunotherapies and immunosuppressants, espouse the presence of an underlying autoimmune process. Prior reports of autoimmune encephalitis in COVID-19 patients may further support the latter, but the role of molecular mimicry and the identity of the culprit spike protein epitope currently remain unknown. Regardless, physicians must remain aware of the rare possibility of developing NORSE from autoimmune encephalitis after receiving tozinameran, so that timely treatment can be administered given its significant propensity for poor clinical outcomes. Importantly, the exceptionally rare occurrence of NORSE compared to the billions of doses of tozinameran already administered, instead bolsters tozinameran's excellent short-term safety profile and low rates of vaccine-related serious adverse events, the risk of the latter being ultimately outweighed by the ostensible benefits of COVID-19 vaccines in reducing viral transmission and ameliorating the disease's severity amongst those infected.[17,18]

DISCLOSURE

Conflict of interest: None

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