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Case Report

Resolution of cryptogenic new onset refractory status epilepticus with tocilizumab

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ABSTRACT

New onset refractory status epilepticus (NORSE) was defined by the International League Against Epilepsy as occurring in patients presenting without a prior diagnosis of epilepsy or other neurological disease, with seizures that persist beyond 24 h. There is still a need to develop new treatment strategies for NORSE, particularly for those patients who are least responsive to conventional medical therapies. We present a case of a young female patient without any medical history presenting with status epilepticus, which was refractory not only to anti-seizure medications and anesthetics, but also to conventional immunomodulatory therapies. After nine weeks of electroclinical seizure activity, the patient responded to two doses of tocilizumab.

1. Introduction

Status epilepticus (SE) is a condition that has recently undergone much clinical scrutiny, with ongoing debate about its definition and diagnostic criteria that include other clinical terms, such as refractory and "super-refractory" status. Most recently, the International League Against Epilepsy (ILAE) proposed SE to be a condition resulting from either initiation of mechanisms leading to prolonged seizure activity and/or failure of mechanisms that terminate seizure activity [1]. Duration of seizure activity is central to these criteria, with 5 minutes being the most widely accepted period at which an individual is diagnosed with convulsive SE, and 30 minutes proposed as the time for "refractory," at which point the risk of permanent neuronal injury becomes significant [1].

While SE is commonly associated with an established diagnosis of epilepsy, there is growing recognition of SE presenting without a prior seizure history and, in some cases, with refractory or super-refractory SE. New Onset Refractory Status Epilepticus (NORSE) is diagnosed in people with SE lacking a previous diagnosis of epilepsy, any concomitant neurological disorder or structural abnormality, or toxic/metabolic disturbance [2]. NORSE is a rare condition, mostly affecting children and young adults [3]. Boys are more commonly affected than girls, but there is a female predominance in adults. NORSE may be preceded by fever or mental status changes, but patients typically present to the hospitals with status epilepticus, most commonly associated with focal motor seizures that may evolve to bilateral convulsive seizures, less frequently in the form of a nonconvulsive status epilepticus [4]. From a treatment perspective, NORSE may respond to anti-seizure medications with or without anesthetics, but as most patients develop super-refractory status, immunomodulatory therapies are often required [3]. The etiology is often unknown, but about 50% of cases appear to be autoimmune or inflammatory in nature [3,4]. This has led to trials of immunosuppressant therapies, such as pulse steroids, intravenous immunoglobulin (IVIG), or plasmapheresis (PLEX), as well as immunomodulating agents, including rituximab, cyclophosphamide, or anakinra, with variable results [3,4]. We present a case of a patient with cryptogenic NORSE, who failed conventional immunosuppressant and immunomodulating therapies, but who finally responded to tocilizumab.

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2. Case history

A twelve-week timeline of diagnostic testing and therapeutic interventions during three consecutive hospitalizations is presented in Fig. 1. A 26-year-old woman was admitted first admitted to an outside hospital following repetitive convulsive seizures. She received lorazepam 2 mg intravenously then 5 mg of intranasal midazolam. She continued to have convulsive seizures without recovery of responsiveness, and while being loaded on levetiracetam and lacosamide, she was intubated and sedated. All of her EEG studies at the first hospital were daily 30-minute studies; her first study after initiation of treatment demonstrated continuous slowing, with recurrence of facial twitching associated with runs of periodic discharges at 1–4 Hz frequency on the second day, bilateral independent left and right hemispheric discharges on the third day, and generalized periodic discharges on the fourth day. She was transferred to a second hospital, where she underwent continuous scalp EEG monitoring, demonstrating predominantly left hemispheric discharges associated with right facial twitching, which frequently evolved into bilateral convulsive seizures. Magnetic resonance imaging (MRI) of her brain was normal and cerebrospinal (CSF) studies, including autoimmune panels, were unremarkable. Malignancy screening with thoracic, abdominal and pelvic CT revealed an ovarian cyst, which, after an oophorectomy, was determined to be histologically benign. Despite trial of multiple anti-seizure medications, including (PHT), phenobarbital (PB), valproic acid (VPA), and clobazam (CLB), and anesthetics, such as propofol, midazolam, ketamine and pentobarbital, her continuous video-EEG monitoring continued to show multifocal, bihemispheric epileptiform discharges with intermittent seizure activity. The frequency and of her seizures, and whether or not the seizures were clinically evident, was not clear from the available records. Immunotherapy was also initiated, including steroids, IVIG, PLEX and a single dose of

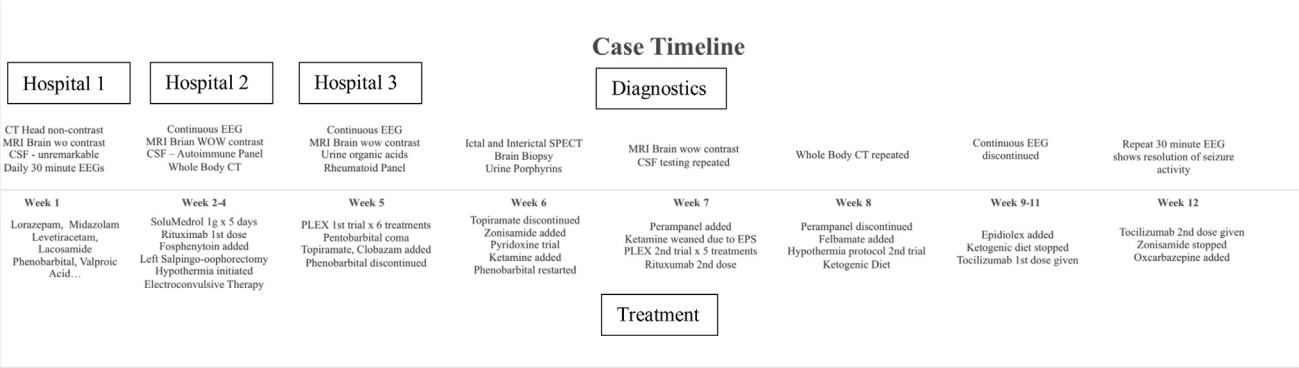

Fig. 1. MRI Brain, With and Without Contrast: small scattered foci of gradient susceptibility on T2* sequence noted in the gray-white matter junction throughout the right cerebral hemisphere (A, B) and left posterior parietal lobe (B). These are not visualized on FLAIR (C) or T1 post-contrast (D).

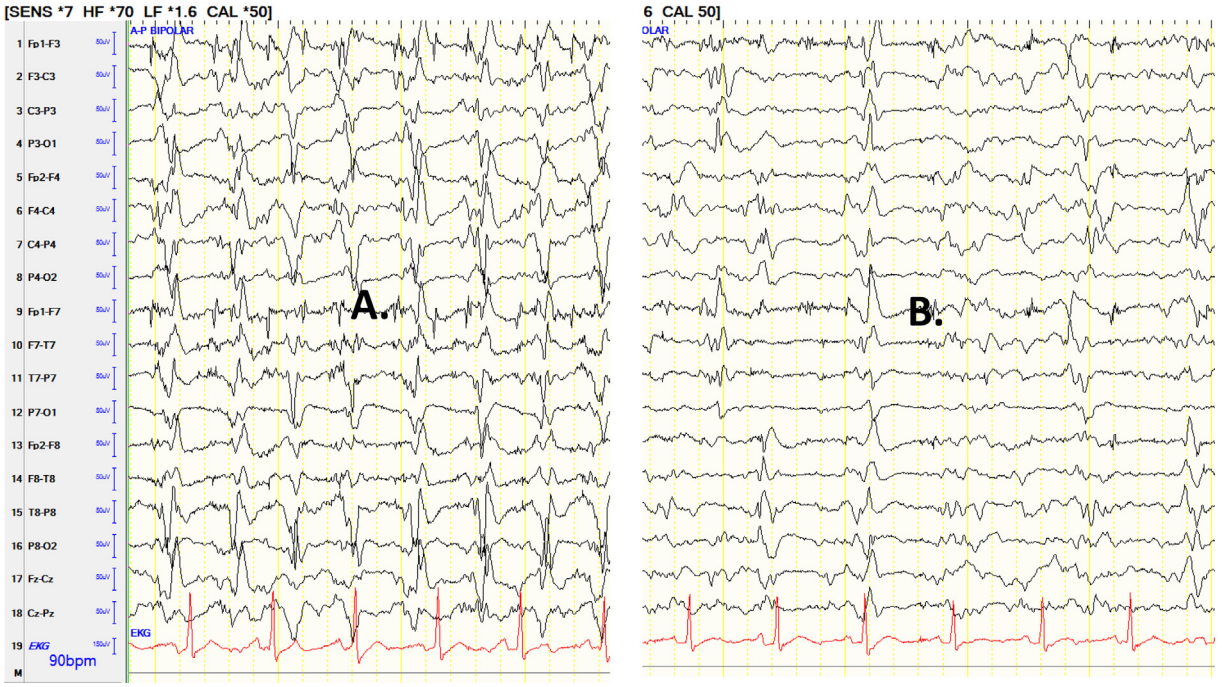

Fig. 2. A, B. Biopsy of frontal lobe cortex and subcortical white matter showed a subtle microvasculopathy characterized by fibrinoid thickening of small vessel walls, which were negative for amyloid on Congo red and Beta-amyloid immunostain (not shown) (H&E, A: 200×, B:400×). C. CD68 highlights activated microglia as well as macrophages and hemosiderin deposition in the perivascular spaces indicative of compromise of the blood brain barrier (CD68, 200×). D. Lymphocytes were limited to the perivascular spaces of small vessels with neither extension into the brain parenchyma nor infiltrating vessel walls (CD45, 400×). (Arrowhead: hemosiderin in perivascular spaces; *: lumen of small vessels; white arrow: activated microglia; black arrow: lymphocytes in perivascular spaces).

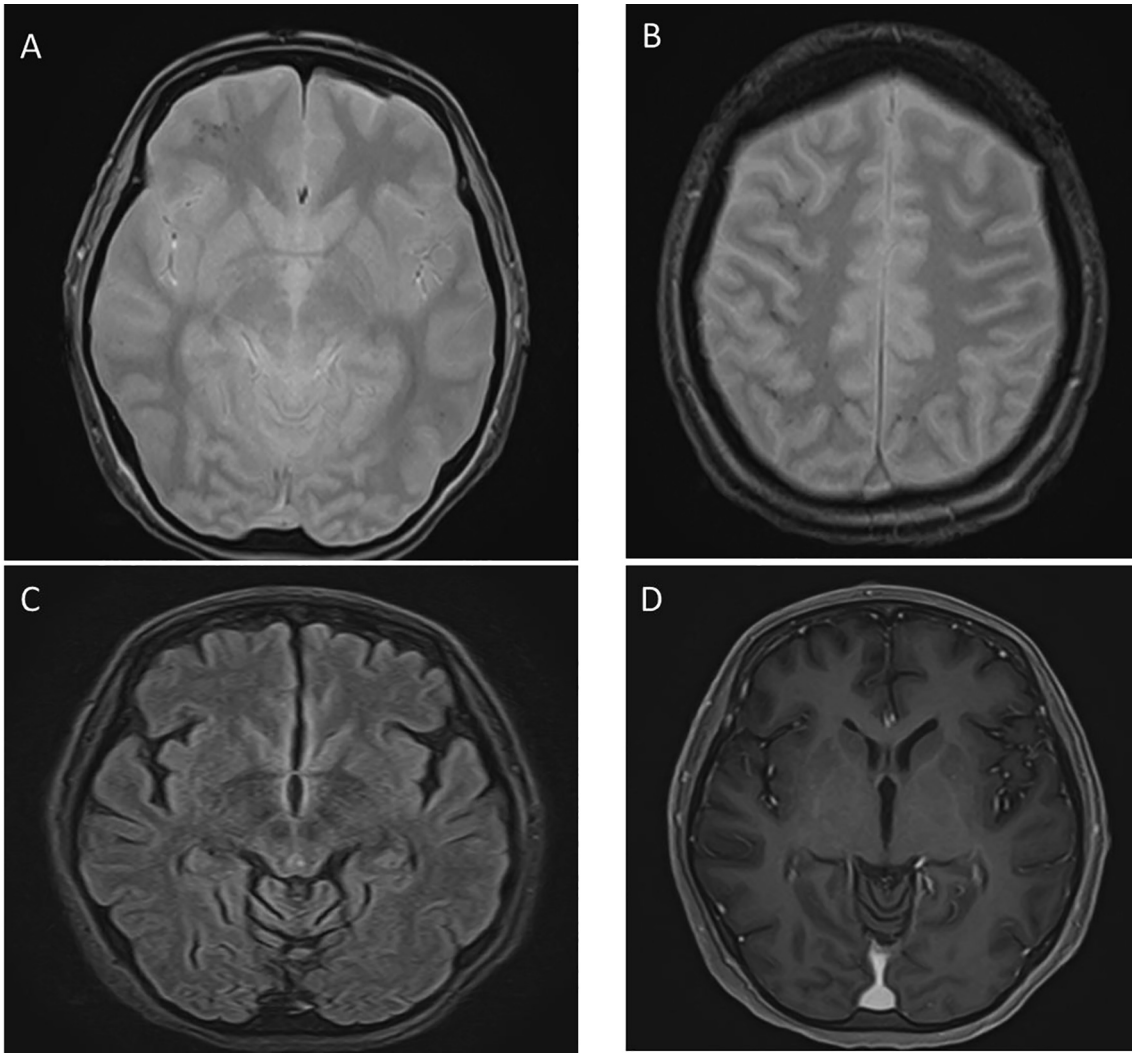

Fig. 3. Brain MRI Findings. MRI Brain with and without contrast: small scattered foci of gradient susceptibility on T2* sequence noted in the gray-white matter junction throughout the right cerebral hemisphere (Panels A, B) and left posterior parietal lobe (Panel B). These are not visualized on FLAIR (C) or T1 post-contrast (D).

rituximab, all without reported benefit. After an unsuccessful trial of hypothermic coma, the patient underwent three trials of electroconvulsive therapy (ECT), the third trial complicated by a cardiopulmonary arrest. After being in SE for six weeks, she was transferred to our institution.

On arrival, continuous EEG monitoring confirmed nonconvulsive SE, characterized 2–3 Hz generalized periodic discharges (Fig. 2A). Her anti-seizure medication regimen consisted of CLB, VPA, LEV, PHT, LCM, and topiramate (TPM). Her EEG background was intermittently suppressed with propofol, pentobarbital, and ketamine (Fig. 2B). She underwent a repeated CSF examination, which did not reveal infection or inflammation (nucleated white blood cell count 12/mcL, red blood cell count 9000/mcL and protein 97 mg/dL), as well as repeat whole body CT to identify a potential neoplasm. A brain MRI demonstrated multiregional punctate microhemorrhages in the subcortical white matter, more diffusely over the right than left hemispheres, consistent with an ICU cerebral angiopathy (Fig. 3). Subtraction analysis of ictal and interictal single photon emission computerized tomography (SPECT) scans demonstrated bihemispheric, multiregional activations, best defined in the right frontal and left medial motor cortices. Based upon the multiregional findings which overlapped in the right frontal lobe, and an intermittent predominance of right hemispheric seizures, a right frontal brain biopsy was performed to identify an underlying etiology. The brain biopsy showed microglial activation and a subtle microvasculopathy characterized by thickened small vessels; reactive CD3 + T-lymphocytes and hemosiderin deposition were also noted within the perivascular spaces, indicating compromise of the blood brain barrier (Fig. 4). Her antiseizure medication regimen was changed to include perampanel (PER), felbamate (FBM), and oxcarbazepine (OXC). She underwent a second round of PLEX and rituximab. Her EEG continued to demonstrate multifocal bihemispheric ictal patterns and interictal epileptic discharges. Decreases in pentobarbital levels resulted in return of repetitive myoclonus of the right foot, left face and hand, as well as recurrence of independent left or right focal motor seizures. Ketogenic diet and Epidiolex (CBD) were also attempted, but there was concern that neither these treatments could be sustained due to transaminitis and hyperammonemia.

After almost nine weeks of treatment for super-refractory SE, a trial of tocilizumab was considered after a literature search [5]. Tocilizumab 300 mg was administered intravenously, and, within 48 hours, the periodic epileptiform discharges resolved. Her focal seizures became clinically more discrete, occurring only 2–4 times per hour, and while anesthetics were weaned, the patient became arousable, even interactive. Due to her rapid recovery, a second

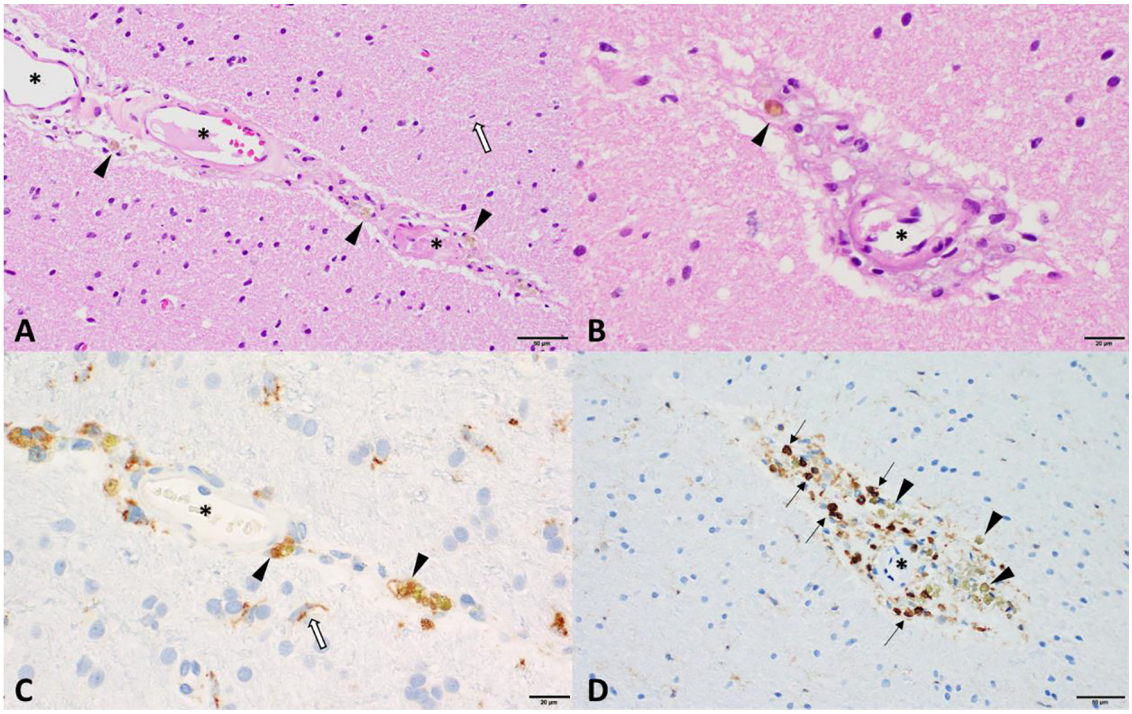

Fig. 4. Histopathological Findings on Brain Biopsy. A and B: Biopsy of frontal lobe cortex and subcortical white matter showed a subtle microvasculopathy characterized by fibrinoid thickening of small vessel walls, which were negative for amyloid on Congo red and Beta-amyloid immunostain (not shown) (H&E, A: 200×, B:400×). Panel C: CD68 highlights activated microglia as well as macrophages and hemosiderin deposition in the perivascular spaces indicative of compromise of the blood brain barrier (CD68, 200x). Panel D: Lymphocytes were limited to the perivascular spaces of small vessels without extension into the brain parenchyma or infiltration of vessel walls (CD45, 400×). (Arrowhead: hemosiderin in perivascular spaces; *: lumen of small vessels; white arrow: activated microglia; black arrow: lymphocytes in perivascular spaces).

dose was not repeated a week later as previously suggested [5]. She was extubated and she improved clinically the following three weeks. At that time, she suddenly exhibited evidence of psychomotor regression with an EEG demonstrating increased and repetitive focal ictal discharges involving either hemisphere. She received a second infusion of 300 mg tocilizumab, leading to the resolution of electroclinical changes, again within 48 h. Due to critical illness myopathy, the patient was discharged to an inpatient rehabilitation facility. Two months after discharge, her neurological examination demonstrated recovery of her cognitive and motor functioning, but with persistent mild cognitive impairment, mainly with short-term memory deficits, lower extremity weakness, and mild ataxia.

3. Discussion

Our patient was treated for super-refractory NORSE for nine weeks in three hospitals. She finally responded to tocilizumab within 48 hours of its administration on two separate occasions. Her case not only confirms the role of immunomodulatory agents in the treatment of NORSE, despite absence of clinical evidence pointing toward an immune-mediated mechanism, but also that the responses of super-refractory NORSE to immunomodulatory agents are variable, with a persistent need to better understand potential clinical markers that may predict a more favorable response to any particular agent. This case study also highlights histopathologic findings of antemortem brain tissue, thereby providing a rare glimpse into possible histopathological mechanisms underlying NORSE (Fig. 4).

In people presenting with SE, NORSE is a diagnosis of exclusion. Our patient presented with refractory SE, associated with bihemispheric and multiregional ictal and interictal epileptic discharges. She underwent several brain MRI scans and whole-body CT examinations, metabolic screening, as well as repeated CSF examinations to identify infectious or auto-immune etiologies, all of which were negative. She was treated pulse steroids, one round of IVIG, followed by two rounds of plasmapheresis and rituximab, respectively. On the verge of considering a trial of cyclophosphamide, we learned about a case series demonstrating the success of tocilizumab in patients who had failed other immunomodulatory and chemotherapies [5], and, as it was likely to be better tolerated than cyclophosphamide, we decided to administer tocilizumab. Furthermore, a repeat CSF examination demonstrating elevation of CSF cytokines, specifically of IL-6, could have provided further support for trying tocilizumab [5].

Tocilizumab therapy for patients with status epilepticus has been limited to case series and case reports [5–8]. One prospective cohort study of seven adult patients with NORSE secondary autoimmune encephalitis was treated with two doses of tocilizumab (4 mg/kg) at least one week apart. They demonstrated cessation of status epilepticus in six patients with a median interval of 3 days from in its initiation. Earlier treatment correlated with better functional outcomes [5]. However, two patients experienced severe adverse events related to infection. It is possible that a using a single dose of tocilizumab may be just as efficacious with less compromise of the immune system. In another case series, two pediatric patients with refractory status epilepticus responded to tocilizumab with favorable functional outcomes, including an improved level of consciousness and recovery of language and motor skills [8].

Tocilizumab is an interleukin-6 (IL-6) receptor antagonist which was initially approved for the treatment of rheumatoid arthritis [9]. Tocilizumab has been used in the treatment of cytokine releasing syndrome, giant cell arteritis and various autoimmune

disorders, most recently in patients with central nervous system autoimmune disorders, such as autoimmune encephalitis [4,6,10]. The role IL-6 in perpetuating status epilepticus is under investigation, but recent studies demonstrated that frequent, repetitive seizures activate an inflammatory cascade associated with a rise in IL-6 levels, leading to disruption of the blood–brain barrier and further inflammation, thereby sustaining seizure activity [11,12]. As elevation of IL-6 may be evident even in the absence of abnormal cell counts or protein levels in the CSF [4,13], measurement of serum or CSF cytokines, including IL-1β, IL-2, IL-4, IL-5, IL-10, IL-12, as well as granulocyte–macrophage colony stimulating and tumor necrosis factors, may be used to direct immunomodulatory therapies and to evaluate their efficacy [4].

In summary, tocilizumab is a potentially effective immunomodulatory therapy for NORSE, even in absence of inflammatory markers in CSF or on brain MRI. Elevation of cytokines in the serum and CSF, and of IL-6 in particular, may encourage earlier intervention with tocilizumab.

4. Study Ethics and patient consent

This study was performed in accordance with "The Code of Ethics of the World Medical Association".

Ethical Statement

Financial disclosures

Jonathan Paul Donnelly reports no disclosures.
Nidhi Kasatwar reports no disclosures.
Shaheryar Hafeez reports no disclosures.
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Charles Akos Szabo reports no disclosures.

Author contributions

JPD and NK designed and conceptualized the report, drafted, and revised the manuscript. SH, AS and CAS supervised the report design and revised the manuscript for intellectual content. AG provided pathology images and reports and edited the manuscript. CB and CS contributed to the pharmacological aspects of the case, report design and edited the manuscript. All authors have viewed the manuscript and agree to submit.

The authors confirm there is no identifiable patient information within this manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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