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Rituximab induced cerebral venous sinus thrombosis in a patient with anti-*N*-methyl-D-aspartate receptor-antibody encephalitis: a case report and review of literature

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Abstract

Background Cerebral venous sinus thrombosis has not been reported in anti-*N*-methyl-D-aspartate receptor-antibody encephalitis in the absence of an underlying thrombotic state while rituximab induced cerebral venous sinus thrombosis is rarely reported. We report a patient with anti-*N*-methyl-D-aspartate receptor-antibody encephalitis without a prothrombotic state who developed cerebral venous sinus thrombosis following rituximab treatment.

Case presentation A 15-year-old Sri Lankan girl who had been in remission following an episode of anti-*N*-methyl-D-aspartate receptor-antibody encephalitis 2 years ago, presented with a relapse of anti-*N*-methyl-D-aspartate receptor-antibody encephalitis characterized by recurrent seizures, mutism, and cognitive abnormalities. Since response was inadequate to first-line immunotherapy, she was administered four doses of rituximab at weekly intervals. Two days after the fourth dose, she developed increasing headaches, and her cranial magnetic resonance venogram confirmed the development of cerebral venous sinus thrombosis. Screening for prothrombotic states were negative. She made an unremarkable recovery following anticoagulation.

Conclusion This case highlights the occurrence of the rare but serious complication of cerebral venous sinus thrombosis following rituximab in the context of anti-*N*-methyl-D-aspartate receptor-antibody encephalitis and informs the clinician to be wary of new onset headache in patients with anti-*N*-methyl-D-aspartate receptor-antibody encephalitis treated with immunotherapy.

Keywords Cerebral venous sinus thrombosis, NMDARE, Rituximab, Sri Lanka

Background

Cerebral venous sinus thrombosis (CVST) is complete or partial occlusion of dural sinus and cerebral veins due to blood clot. It clinically manifests as headache, vomiting, impaired consciousness, seizures, and focal neurological signs [1]. CVST results from venous stasis, vessel wall damage, and/or a hypercoaguable state. CVST has multifactorial etiologies including infection, inflammation, dehydration, prothrombotic conditions, pregnancy, malignancy, head injury, and drugs [1]. The autoimmune

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conditions commonly associated with CVST are Behcet disease, systemic lupus erythematosus (SLE), Sjögren syndrome, and antiphospholipid antibody syndrome (APLS) [2].

Anti-*N*-methyl-D-aspartate receptor (NMDAR)-antibody encephalitis (NMDARE), first described in 2005, has now emerged as the third most common cause of encephalitis after viral encephalitis and acute disseminated encephalomyelitis (ADEM) [3]. It is mediated by IgG antibodies against the GluN1 subunit of the NMDA receptors in the brain and predominantly affect children and adolescents. The disease has a characteristic multistage progression from cognitive and psychiatric manifestations to seizures, movement disorders, and coma [3] but has a good outcome if treated early. Initial treatment includes intravenous methyl prednisolone (IVMP), intravenous immunoglobulins (IVIG), or plasma exchange (PLEX), while rituximab and/or cyclophosphamide are used as second line treatment.

CVST has not been reported in association with NMDARE in the absence of an associated prothrombotic state [4–6], while CVST associated with rituximab has been previously reported only seven times [10–16]. We report the first case of CVST associated with rituximab treatment in NMDARE and review relevant literature.

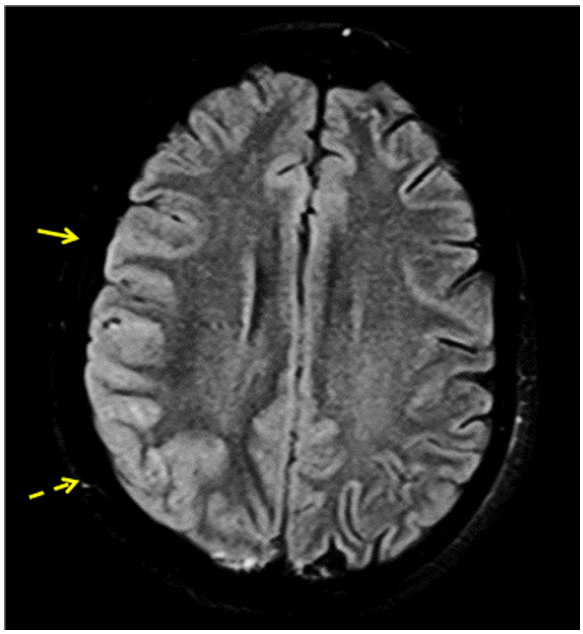

Fig. 1 Magnetic resonance imaging shows cortical thickening and sulcal effacement involving right posterior frontal (arrow) and parietal lobes (dashed arrow) with high T2/FLAIR signal intensity

Case report

A 15-year-old Sri Lankan girl, who had been diagnosed with NMDARE 2 years previously, presented with altered behavior and reduced speech for 1 week. At her initial presentation 2 years ago, she had been treated with IVMP and PLEX but did not require long term maintenance immunotherapy. She had been reasonably well until this presentation apart for regressed school academic performance. After admission to hospital this time, she developed focal seizures and orofacial dyskinesia while she became increasingly mute but agitated. She did not develop fever or manifest any stigmata of connective tissue disorders. The neurological examination was unremarkable.

Her full blood count, renal and liver profile, and inflammatory markers were normal. Magnetic resonance imaging (MRI) showed abnormal thickening and increased signal intensity in the left caudate nucleus, putamen, and insular cortex (Fig. 1). Signal changes were also noted in left cerebellar hemisphere with additional diffusion restriction. The features were compatible with encephalitis mainly involving right cerebral hemisphere and left cerebellar hemisphere. Cerebrospinal fluid (CSF) analysis

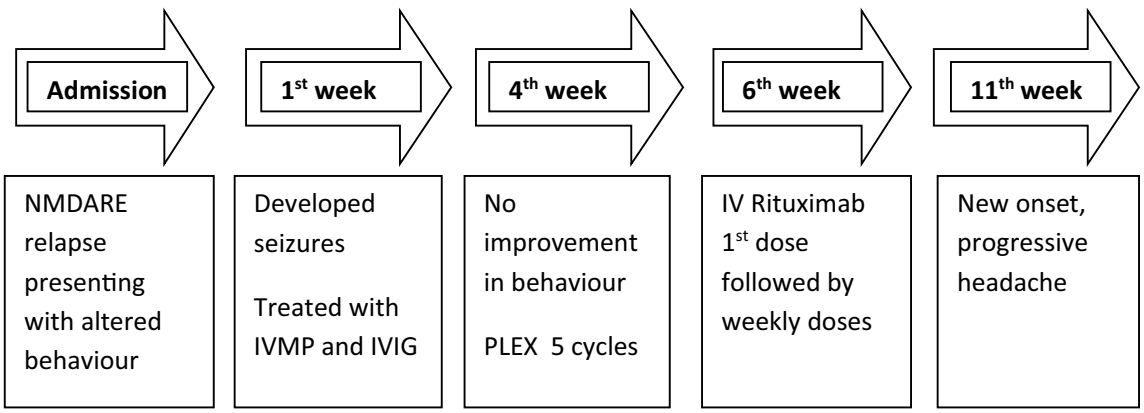

Fig. 2 Timeline of events

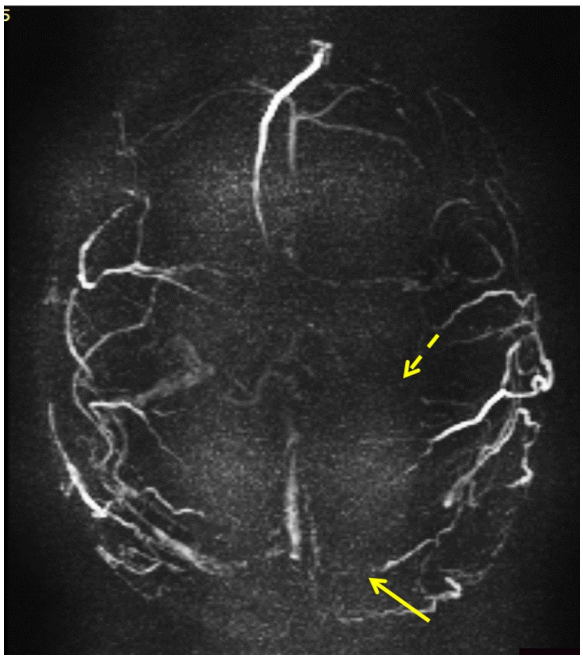

Fig. 3 Cranial magnetic resonance venogram shows cerebral venous thrombosis of left transverse sinus (arrow) and sigmoid sinus (dashed arrow)

was normal, but NMDAR antibodies were detected in CSF. Contrast enhanced computed tomography (CT) abdomen and pelvis did not reveal any teratomas.

A diagnosis of a relapse of NMDARE was made and treated with IVIG 0.4 g/kg/day and IVMP 1 g/day for 5 days, followed by oral prednisolone 1 mg/kg, with which her seizures stopped but with minimal improvement in behavior. Rituximab was delayed due to infection and antibiotic induced liver injury. In the meantime, her seizures recurred, and five cycles of PLEX were done 21 days after completion of IVIG. After completion of PLEX, four weekly doses of 500 mg of rituximab were administered during her hospital stay.

She had a remarkable improvement in behavior and was seizure free following rituximab but complained of a new onset severe headache 2 days after the fourth dose of rituximab, in her 11th week of illness. She did not develop fever or vomiting, and the neurological examination remained unremarkable. Her optic fundi were not visualized due to poor cooperation (Fig. 2).

Her cranial magnetic resonance venogram (MRV) showed cerebral venous sinus thrombosis in the left transverse and sigmoid sinuses (Fig. 3), while MRI showed resolving encephalitis.

Her anti-cardiolipin antibodies, anti-nuclear antibodies (ANA), β2 glycoprotein, protein C, S, antithrombin III activity, and factor V Leiden were all normal. She was commenced on anticoagulation with enoxaparin and warfarin. Her headache resolved after 7 days, and she showed progressive improvement.

As this patient did not have evidence of any prothrombotic states, CVST was thought to be provoked by rituximab. Follow-up MRV at 6 months showed complete resolution of the CVST, and warfarin was discontinued at 6 months. Immunotherapy was continued with mycophenolate mofetil combined with tapering doses of oral prednisolone.

Discussion

Rituximab has emerged as an effective treatment of NMDARE and is increasingly being used as first-line therapy, particularly if response to IVIG, IVMP, and PLEX is delayed or inadequate. CVST has been recognized as a rare complication of rituximab treatment while there are only three reports of CVST associated with NMDARE in patients thought to have an associated prothrombotic state (Table 1). We report a patient with NMDARE without a prothrombotic state who developed CVST 2 days after the fourth dose of rituximab.

In the first report of CVST-associated NMDARE, the patient was diagnosed with coexisting antiphospholipid antibody syndrome (APLS) [4], and in the second report, the patient had increased factor 8 levels [5], both of which are prothrombotic states that predispose to CVST. In the third report, the patient had been noticed to have CVST on admission and subsequently NMDARE was diagnosed. However, the causes for CVST in this patient had not been evaluated [6]. The scarce literature indicates that NMDARE, per se, is unlikely to cause CVST. Moreover, our patient developed CVST while her encephalitis changes were resolving as was evident in the MRI.

Multiple treatment modalities of NMDARE are associated with a procoagulant state. IVIG is known to cause deep vein thrombosis by hyperviscosity and reduced capillary flow. Even though the half-life of IVIG is 21 days, and delayed thrombosis has been reported, thrombotic risk is more during the first week of treatment [7, 8]. This patient developed CVST almost 10 weeks post-IVIG. She was also given PLEX after 21 days of IVIG, which would have eliminated the remaining immunoglobulins in the circulation. Therefore, IVIG induced hyperviscosity causing CVST appear unlikely in this patient.

High-dose steroids usage is associated with deep vein thrombosis and pulmonary embolism with the highest risk noted in the first month post treatment [9]. The exact mechanism of exogenous steroids causing thrombosis remains unclear, but patients on steroids have been found to have increased levels of fibrinogen, Von Willebrand

Table 1 Case reports of cerebral venous sinus thrombosis in patients with anti-*N*-methyl-D-aspartate receptor encephalitis

Reference	Age (years), Sex	Extent and timing of CVST	Prothrombotic state	Type of immunotherapy	Outcome
Hsu *et al*. [4]	20, male	Left transverse sinus thrombosis 3 weeks after encephalitis	APS	PLEX, hydroxychloroquine	Free of neurological symptoms and thrombosis
Gagan Singh *et al*. [5]	23, female	Right transverse sinus thrombosis after 2 weeks of psychiatric symptoms	Increased factor 8	Steroids	Improved mentation but persisting word finding difficulty and gait instability
Naveed Ullah Khan *et al*. [6]	18, male	Superior sagittal, left transverse and sigmoid sinus thrombosis followed by encephalitis	Not evaluated	PLEX, steroids	Improved neurological symptoms and seizure freedom

APS antiphospholipid syndrome, *CVST* cerebral venous sinus thrombosis, *PLEX* plasma exchange

factor (VWF), and thrombin [10]. This patient developed CVST 2 months after initiation of steroids. Although delayed, steroid treatment may have contributed in part to the development of her CVST.

Thrombosis has been reported as a complication of rituximab, an anti-CD20 monoclonal antibody. In a series of 38 patients with low grade lymphoma treated with rituximab, one patient developed venous thrombosis [11]. Trials of rituximab in pemphigus vulgaris reported seven cases of venous thromboembolism (VTE) following 2–10 weeks of the first rituximab infusion [12–16]. Two multicenter randomized control trials that assessed rituximab in immune thrombocytopenia reported thrombosis in four patients in the treatment arm compared with none in the placebo arm [17]. The duration of VTE from first rituximab infusion varied from 7 to 125 weeks. In this patient, the temporal relationship between the first rituximab dose and development of CVST was 5 weeks, and CVST was attributed to rituximab after exclusion of prothrombotic states and connective tissue disorders.

The mechanism of thrombosis associated with rituximab remains unclear, but complement activation by immune complexes of rituximab and human antichimeric antibody increasing the thrombotic risk has been suggested [18]. It is also proposed that thrombocytopenia noted following rituximab might probably be related to thrombocyte aggregation [19]. Thrombocytopenia did not occur in this patient.

Conclusion

This case highlights the occurrence of the rare but serious complication of CVST following rituximab in the context of NMDARE and informs the clinician to be wary of new onset headache in patients with NMDARE treated with immunotherapy.

Abbreviations

ADEM	Acute disseminated encephalomyelitis
ANA	Antinuclear antibody
APLS	Antiphospholipid syndrome
CNS	Central nervous system
CSF	Cerebrospinal fluid
CT	Computed tomography
CVST	Cerebral venous sinus thrombosis
IgG	Immunoglobulin G
IVMP	Intravenous methylprednisolone
IVIG	Intravenous immunoglobulin
MRI	Magnetic resonance imaging
MRV	Magnetic resonance venography
NMDAR	Anti-*N*-methyl-D-aspartate receptor
NMDARE	Anti-*N*-methyl-D-aspartate receptor encephalitis
PLEX	Plasma exchange
SLE	Systemic lupus erythematosus
VTE	Venous thromboembolism
VWF	Von Willebrand factor

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All authors contributed equally to the management of the patient and contributed to the drafting of the manuscript. SM wrote the first draft of the manuscript. RT and TC critically appraised the manuscript while TC prepared the final version. All authors read and approved the final manuscript.

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Declarations

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Competing interests
The authors declare that they have no competing interests.

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