Investigation into the casual or causal association of cerebral venous thrombosis and myelin oligodendrocyte glycoprotein antibody-associated disease: A case report and literature review

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Abstract. Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is a central nervous system demyelinating syndrome (DS) typically presenting with optic neuritis or myelitis. The association between cerebral venous thrombosis (CVT) and demyelinating diseases, including multiple sclerosis (MS), is rare. In the present study, a 37-year-old man presented with sensory disturbances in the lower limbs and urinary incontinence, consistent with myelitis. The diagnosis of MOGAD was confirmed by spinal magnetic resonance imaging findings and serum anti-MOG antibody positivity using a cell-based assay. The patient responded successfully to intravenous corticosteroid therapy. However, shortly after recovery, the patient developed a persistent headache and suffered an epileptic seizure, which was later attributed to CVT. The patient was treated with low molecular weight heparin and lacosamide and subsequently returned to baseline health status without seizure recurrence in the following year. Comprehensive review of the literature on CVT associated with DS, encompassing 15 case reports, two case series and two studies, underscores the rarity of this condition. Most reported cases of CVT have been linked to MS, while only three cases of CVT associated with MOGAD have been documented to date. Additional risk factors, such as lumbar puncture and high-dose corticosteroid treatment, have been implicated in some instances. Given their shared inflammatory basis, a thrombotic-inflammatory pathogenic mechanism acting between DS and CVT in predisposed individuals is plausible. However, the exact pathogenic association between these conditions remains largely unclear, and a coincidental association cannot be ruled out. The role of anti-MOG antibodies in this rare condition also warrants further investigation.

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Abbreviations: AQP4, aquaporin-4; CVT, cerebral venous thrombosis; LETM, longitudinally extensive myelitis; LP, lumbar puncture; MOGAD, myelin oligodendrocyte glycoprotein-associated disease; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder

Key words: demyelinating disorders, MS, MOGAD, cerebral sinus thrombosis

Introduction

Myelin oligodendrocyte glycoprotein-associated disease (MOGAD) is a rare autoimmune inflammatory demyelinating disorder, distinct from multiple sclerosis (MS) and aquaporin-4 (AQP4)-seropositive neuromyelitis optica spectrum disorder (NMOSD). MOGAD can affect individuals of any age, with the highest incidence in children, and an equal distribution between males and females (1). The incidence of MOGAD ranges from 1.6 to 3.4 cases per million individuals per year, with an estimated prevalence of 20 cases per million (2). Clinical manifestations are diverse and include optic neuritis, transverse myelitis, acute disseminated encephalomyelitis, and encephalitis predominantly involving the cortex, brainstem and cerebellum (2). Approximately one-half of the patients experience a monophasic disease course, but relapses are also possible. Serum immunoglobulin G (IgG) antibodies against MOG, a protein expressed on the surface of central nervous system (CNS) myelin sheaths, are considered the hallmark of the disease. A prodromal infectious disease is considered to trigger an autoimmune response against the CNS through mechanisms such as molecular mimicry or epitope spreading (1). The gold-standard treatment of acute phase attacks is based on high-dose glucocorticoids. Plasma exchange or intravenous immune globulin are suggested for refractory cases or incomplete responses. Immunosuppressive therapy is typically reserved for patients with relapsing disease (3). Autoimmune diseases are recognized as a risk factor for cerebral venous thrombosis (CVT), which is an uncommon cause of stroke (4,5). To date, few cases of CVT

have been reported in the context of MS (6), and only three cases in association with MOGAD (6,7). The present study reports a case of CVT occurring in an adult with MOGAD.

Case report

A healthy, 37-year-old man who was a non-smoker presented to the Neurology Unit of 'Bianchi-Melacrino-Morelli' Hospital (Reggio Calabria, Italy) with a 2-week history of asthenia, gait difficulties, numbness of the lower limbs and urinary urgency. There was no history of recent vaccination, fever or systemic infections. Neurological examination revealed sensory ataxia, brisk tendon reflexes in all four limbs and hypoesthesia extending from the thoracic region (corresponding to the C5 sensory level) to the lower limbs. An urgent spinal magnetic resonance imaging (MRI) scan (Fig. 1) showed a T2- and short-TI inversion recovery-hyperintense, continuous cord lesion from C2 to T1, without contrast enhancement (CE), consistent with longitudinally extensive myelitis (LETM). Additional multiple smaller dorsal cord hyperintensities showed CE, whereas brain and orbital MRI findings were normal. Blood tests revealed mild neutrophilic leukocytosis. A broad infectious and autoimmune work-up, including a COVID-19 test and antinuclear antibodies, was unremarkable. Cerebrospinal fluid (CSF) analysis of a specimen from a lumbar puncture (LP) revealed elevated protein levels (100 mg/dl; normal value, <43 mg/dl), with normal leukocyte count, CSF/serum albumin ratio and glucose levels. The CSF-Film Array assay was performed by the Department of Pathology of 'Bianchi-Melacrino-Morelli' Hospital and was negative for common infectious agents. No intrathecal-restricted synthesis of IgG oligoclonal bands was detected in the CSF. Serum anti-MOG antibodies, tested by the Department of Pathology of 'Bianchi-Melacrino-Morelli' Hospital using a fixed cell-based assay, were positive at a titer of 1:100, whereas antibodies against AQP4 in both CSF and serum were absent.

A diagnosis of MOGAD was made according to the International MOGAD Panel criteria (1), based on a core clinical demyelinating event (myelitis) with supporting MRI features of LETM, positive MOG-IgG antibodies and seronegative AQP4-IgG, after excluding alternative diagnoses. The patient underwent high-dose intravenous methylprednisolone therapy (1,000 mg per day for 5 days), followed by oral prednisone (50 mg daily). The patient fully recovered and was discharged after 10 days with a prescribed tapering of prednisone over 1 month. However, at 3 days post-discharge, the patient returned to the Emergency Department of 'Bianchi-Melacrino-Morelli' Hospital due to a focal to bilateral epileptic seizure, preceded by 2 days of continuous right frontotemporal headaches. Neurological examination revealed mild left hemiparesis and drowsiness, with a National Institutes of Health Stroke Scale (NIHSS) score of 4 (7). An urgent brain computed tomography scan showed a right cortical parietal hypodense lesion. Brain MRI revealed a fluid-attenuated inversion recovery-hyperintense right frontoparietal lesion, and an MRI angiogram showed absence of flow in the right superficial cortical veins and superior sagittal sinus, confirming CVT (Fig. 2).

Blood work-up for thrombophilia, including antinuclear antibodies, factor V Leiden and prothrombin mutation, and deficiencies in antithrombin, protein C and protein S, was unremarkable. Tests for COVID-19 and serum autoantibodies associated with antiphospholipid syndrome, systemic lupus erythematosus and Behçet's disease were also negative. Paroxysmal nocturnal hemoglobinuria was excluded. The patient was treated with subcutaneous low molecular weight heparin (4,000 IU, subcutaneously, twice daily) for 10 days and lacosamide (200 mg per day for 3 months) to prevent seizure recurrence. The patient achieved a complete recovery within 30 days and was discharged with 50 mg/day prednisone, which was slowly tapered and discontinued after 3 months. The patient's clinical condition remained stable over the following year, with unchanged MRI results at the 6- and 12-month follow-ups.

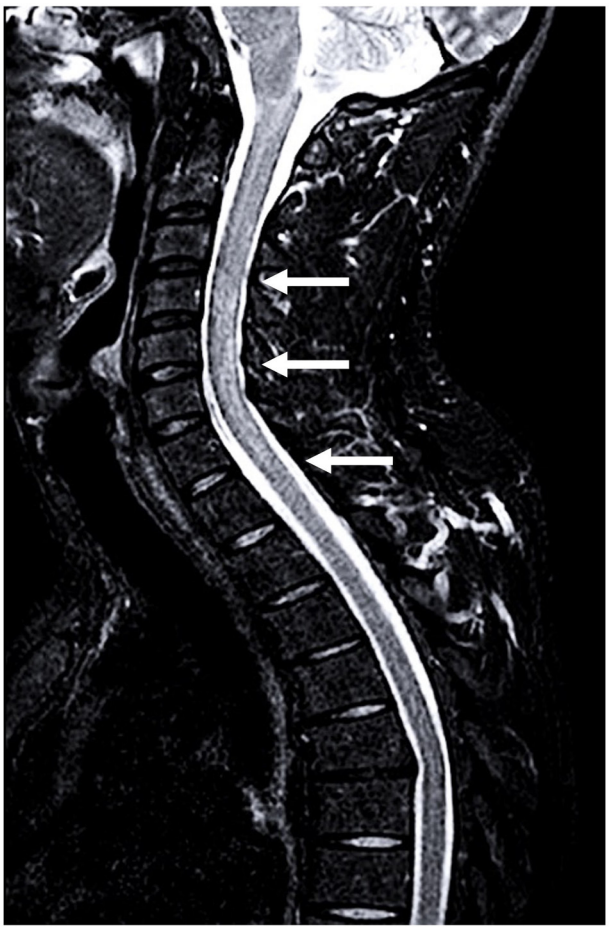

Figure 1. Spine magnetic resonance imaging. Hyperintense cervical cord lesions (arrows) in short-TI inversion recovery sagittal sequences.

Discussion

The present report describes the rare co-occurrence of CVT in a patient diagnosed with MOGAD. The patient developed CVT in the context of an acute MOGAD attack shortly after undergoing a LP and receiving intravenous corticosteroids. Although the coincidental coexistence of MOGAD and CVT in the same patient should be considered, exploring the possible association is of interest due to the inflammatory nature of both conditions. The association between CVT and demyelinating syndromes (DS) has been infrequently reported in the literature.

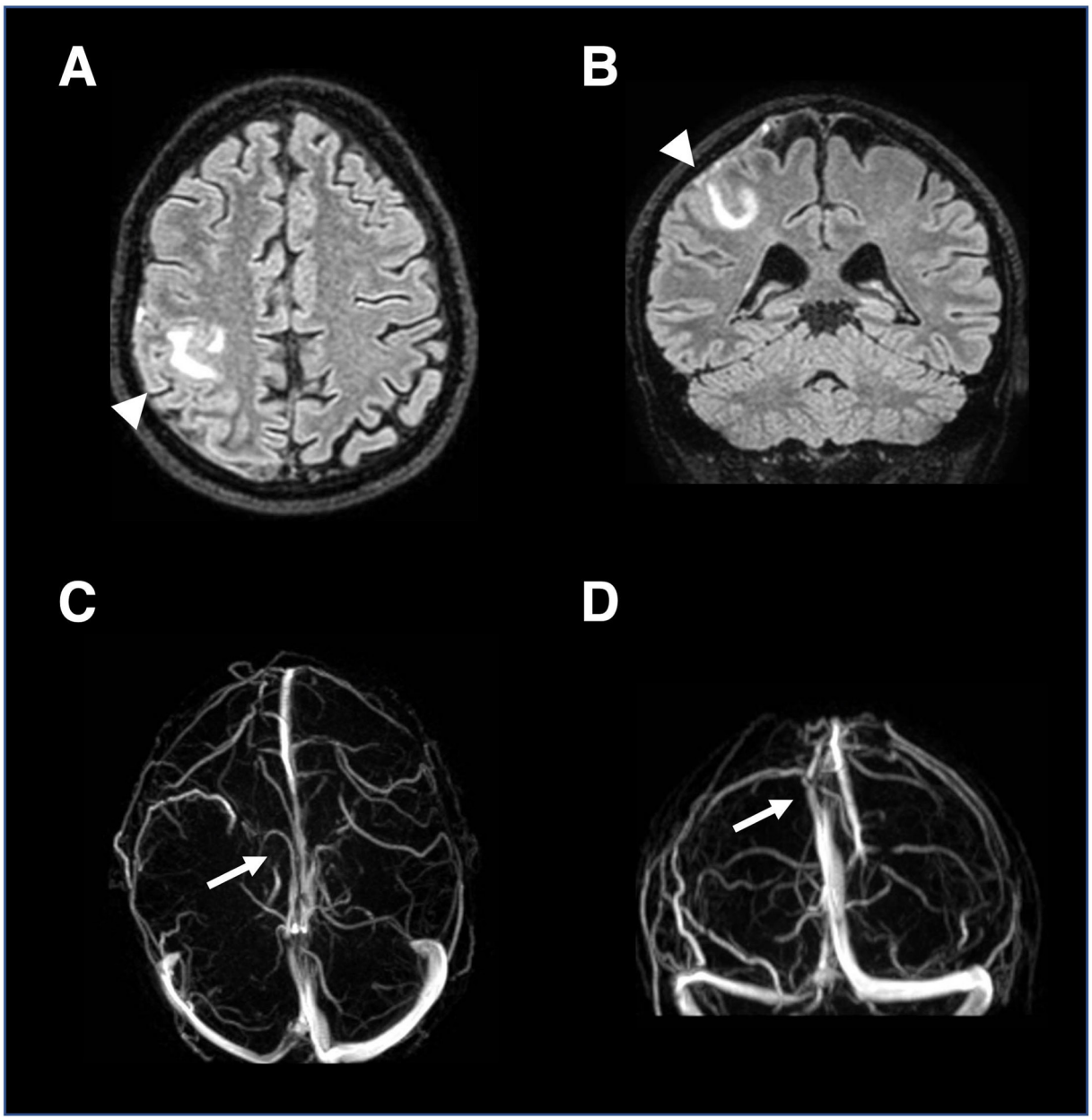

Figure 2. Brain MRI and MR venography findings. MRI (A) axial and (B) coronal sequences showing right parietal fluid-attenuated inversion recovery hyperintensity involving postcentral and precentral gyri (arrowhead). MR venography displaying superior sagittal sinus stenosis (arrows) in (C) axial and (D) coronal views. MR, magnetic resonance; MRI, MR imaging.

A review of the literature was performed using the terms 'MOGAD' OR 'Myelin oligodendrocyte glycoprotein-associated disease' OR 'Multiple Sclerosis' OR 'MS' OR 'anti-MOG' OR 'neuromyelitis optica spectrum disorder' OR 'NMOSD' OR 'demyelinating disorder', in various combinations with 'cerebral venous thrombosis' OR 'cerebral venous sinus thrombosis', in PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Google Scholar (https://scholar.google.com/) up to October 2024. Primary studies, case reports and case series were included, and English was the only language selected. A total of 19 studies were identified, nearly all of which were case reports, reporting a total of 31 patients with CVT associated with MS (26 patients), NMOSD (2 patients) or MOGAD (3 patients) (Table I) (6-25). Only 9 patients exhibited the most common risk factors for CVT (oral contraceptives in 8 cases and inherited prothrombotic disorders in 1 case) (6,10,12,13,18,19,21). In ~84% of cases, procedures such as LP and high-dose corticosteroid administration were reported, highlighting their role as predisposing factors for CVT development (6,19,21,12).

Dural puncture is a rare but well-known risk factor for CVT. While the exact mechanism remains unclear, it is likely associated with intracranial hypotension, leading to venous dilation, displacement of intracranial vascular structures, stasis and congestion, thereby promoting a thrombotic process (12). A potential procoagulant effect of high-dose steroids in CVT development has also been suggested. This is primarily attributable to vascular endothelial cell injury and a hypercoagulable state, characterized by increased prothrombotic factors and impaired fibrinolytic activity, similar to what

Table I. Review of the literature for reported cerebral venous thrombosis cases in patients with demyelinating disorders.

First author, year	Study design	Patients, n	Sex	Age, years	DS type	Risk factors for CVT	CVT symptoms	CVT outcome	(Refs.)
Malanga and Gangemi, 1994	Case report	1	F	35	MS	Oral contraceptive	Seizure	Recovery	(10)
Al Bunyan and Ogunniyi, 1997	Case report	1	F	32	MS	Bed confinement	Asymptomatic	Recovery	(11)
Aidi *et al*, 1999	Case report	2	F	30, 36	MS	Oral contraceptive (n=1), LP (n=2), high-dose i.v. corticosteroid (n=2)	Headache, diplopia	Recovery	(12)
Albucher *et al*, 1999	Case series	3	2 F, 1 M	28, 45, 38	MS	Oral contraceptive (n=1), LP (n=2), high-dose i.v. corticosteroid (n=3)	Headache, seizure, focal motor deficit	Recovery	(13)
Städler *et al*, 2000	Case report	2	n.a.	n.a.	MS	LP, high-dose i.v. corticosteroid (n=2)	n.a.	Death (n=1), recovery (n=1)	(14)
Gunal *et al*, 2002	Case report	1	F	39	MS	LP, high-dose i.v. corticosteroid	Headache, seizures, hemianopia	Recovery	(15)
Mouraux *et al*, 2002	Case report	1	F	35	MS	LP	Headache, seizures, hemiparesis	Recovery	(16)
Kadayifçilar *et al*, 2003	Case report	1	F	44	MS	Oral contraceptive, high-dose i.v. corticosteroid	Headache, hemianopia and hemiparesis	n.a.	(17)
Stolz *et al*, 2003	Observational study	6	n.a.	n.a.	MS (4), NMOSD (2)	High-dose i.v. corticosteroid (n=6), LP (n=3) oral contraceptive (n=3), smoking (n=4)	Headaches (5), seizures (4), focal motor deficits (3)	n.a.	(18)
Vandenberghe *et al*, 2003	Case series	3	2 F, 1 M	40, 23, 49	MS	No risk factor (n=2); oral contraceptive (n=2), high-dose i.v. corticosteroid (n=2), LP (n=2)	Seizure, headache, focal motor deficit	n.a.	(6)
Maurelli *et al*, 2005	Case report	1	F	48	MS	LP, high-dose i.v. corticosteroid	Headache, tetraparesis, coma, seizure	Recovery	(19)

Table I. Continued.

First author, year	Study design	Patients, n	Sex	Age, years	DS type	Risk factors for CVT	CVT symptoms	CVT outcome	(Refs.)
Kalanie *et al*, 2011	Prospective study	2	F	35, 39	MS	High-dose i.v. corticosteroid (n=2)	n.a.	n.a.	(20)
Presicci *et al*, 2013	Case report	1	F	13	MS	Thrombocytosis, thrombophilia, LP, high-dose i.v. corticosteroid	Headache, seizure	Improvement	(21)
Gazioglu *et al*, 2013	Case report	1	F	32	MS	High-dose i.v. corticosteroid	Headache	Recovery	(22)
Soto-Insuga *et al*, 2016	Case report	1	F	6	MOGAD	Infection (otitis)	Headache, diplopia	Recovery	(8)
Gasparini *et al*, 2020	Case report	1	M	40	MS	Alemtuzumab	Headache	Recovery	(23)
Fontana *et al*, 2021	Case report	1	M	11	MOGAD	LP, high-dose i.v. corticosteroid	Headache, facial tics	Recovery	(9)
Zhu *et al*, 2023	Case report	1	F	19	MS	High-dose i.v. corticosteroid	Headache	Improvement	(24)
Virupakshaiah *et al*, 2024	Case report	1	M	35	MOGAD	High-dose i.v. corticosteroid	Focal motor deficit, speech disturbance, impaired consciousness	Improvement	(25)

CVT, cerebral venous thrombosis; DS, demyelinating disorders; LP, lumbar puncture; i.v., intravenous; MOGAD, myelin oligodendrocyte glycoprotein-associated disease; MS, multiple sclerosis; n.a., not available; NMOSD, neuromyelitis optica spectrum disorder.

is observed in Cushing's syndrome (22,24,12). Accordingly, the administration of high-dose intravenous methylprednisolone and LP might have contributed to CVT development in the present case. However, the occurrence of CVT is reported in only a small percentage of individuals exposed to LP or corticosteroids, suggesting that additional risk factors are likely involved.

Moreover, cases of DS-associated CVT occurring without corticosteroid exposure or other recognized risk factors have been described (6,23). Given the shared inflammatory origin of both conditions, a thrombotic-inflammatory pathogenic mechanism between MOGAD and CVT in susceptible individuals is plausible (8,24). The autoimmune and inflammatory pathways implicated in DS may play a role in CVT pathogenesis (5,6,12). The interplay between inflammation, demyelination and coagulation, however, remains poorly understood. The presence of lymphocytic infiltration surrounding veins in DS supports evidence of vascular inflammation (6). Immune-mediated and inflammatory processes in DS may lead to endothelial dysfunction. Cytokines released during inflammation, such as IL-6 (25), could activate the clotting cascade, increasing the likelihood of CVT. Additionally, the severe and often rapid progression of MOGAD could result in brain swelling or lesions that compress adjacent venous sinuses, impairing blood flow and predisposing to thrombosis (25). Vascular damage, coupled with inflammation-induced hypercoagulability, may contribute to CVT development (5).

Despite these observations, the pathogenic association between these two conditions remains largely unknown. To date, there is insufficient evidence to confirm that MOGAD leads to CVT, and a fortuitous association cannot be excluded. Although CVT is rare in DS, the present case underscores the importance of closely monitoring patients for new or worsening headaches and the onset of epileptic seizures. Additionally, patients with MOGAD and identified pro-thrombotic conditions may benefit from careful observation and preventive measures, such as adequate hydration, to reduce CVT risk.

Only 1 year of follow-up was performed in the present study, which limits our understanding of long-term health in patients with MOGAD after CVT, as well as the assessment of disease progression and management strategies.

In conclusion, the current study presents a rare case of MOGAD with CVT in an adult patient. To date, the causal association between MOGAD and CVT lacks compelling evidence. Corticosteroid therapy and LP represent potential mediators or confounding factors, but the possible role of anti-MOG antibodies and the inflammatory pathways occurring in DS should be better ascertained in this uncommon condition. Further studies on pathophysiological mechanisms are required to establish whether a direct causal association exists.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

OM and AP were responsible for study concept and design. Data curation, collection, analysis and interpretation was performed by OM, AP, RC, DT, AB and EF. OM, AP and SG drafted the manuscript. UA and SG advised on patient treatment, revised the manuscript critically for important intellectual content and gave the final approval of the version to be published. OM and AP confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study was performed following the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from the patient.

Patient consent for publication

The patient provided written informed consent concerning the publication of the case report and accompanying patient diagnostic images.

Competing interests

The authors declare that they have no competing interests.

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