Cranial Nerve Involvement Apart from Optic Nerve in MOG-Antibody Disease: Putative Mechanisms

Sir,

Myelin-oligodendrocyte glycoprotein antibody (MOGAD) is a newly characterized immune-pathogenic entity distinct from multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD). It is primarily diagnosed based on the positivity of new-generation cell-based assays, which can detect full-length human myelin-oligodendrocyte glycoprotein (MOG-IgG).[1] The clinical spectrum of the disease is rapidly expanding. The common clinical presentations include optic neuritis, transverse myelitis, acute disseminated encephalomyelitis, and brainstem encephalitis. Rare presentations include cortical encephalitis, peri-optic neuritis, and isolated caudal myelitis.[2] Cranial nerve involvement apart from the optic nerve is rarely reported in MOGAD, with an incidence of approximately 1.1% in a retrospective series.[3] However, little is known about the commonly involved nerves and radiological features. Here, we describe a case of relapsing MOGAD with multiple cranial nerve involvement, review similar cases from the literature, and discuss the putative mechanisms.

A 23-year-old female, a known patient of MOGAD, presented in June 2022 with a 2-week history of bilaterally decreased hearing acuity, speech and swallowing difficulty, and decreased taste perception. General examination revealed cushingoid features. Neurological examination revealed mixed features of pseudobulbar and cerebellar dysarthria, bilateral optic atrophy, and gaze-evoked nystagmus with normal ocular motility. We also noted decreased right-sided facial sensation; absent corneal and conjunctival reflex; left-sided upper motor neuron-type facial weakness; decreased taste sensation; bilateral sensorineural hearing loss; and normal palatal, tongue, and neck muscles. Motor system examination revealed spasticity of both the upper and lower limbs, normal power, exaggerated deep tendon reflexes, and bilateral extensor plantar response. In addition, hemi-anesthesia, bilateral appendicular ataxia, and spastic-ataxic gait were observed. EDSS was 6.5. Magnetic resonance imaging (MRI) of the brain showed patchy T2/FLAIR hyperintensities in the brainstem and bilateral middle cerebellar peduncles and confluent hyperintensities in the cerebellar white matter with patchy enhancement. In addition, small foci of enhancement were seen in the cisternal and intra-canalicular segments of the bilateral VII-VIII nerves and the cisternal segment of the right trigeminal nerve [Figure 1a, 1b]. She first noticed the symptoms in 2013 and developed five relapses, including the current event. While three attacks had cranial nerve involvement clinically or radiologically [Figure 1a-d], all showed brainstem involvement [Figure 1e-h]. The course of the disease is shown in Figure 2. Cerebrospinal fluid (CSF) analyses revealed lymphocytic pleocytosis with mildly elevated protein levels. Serum antinuclear antibody, serum and CSF angiotensin-convertase enzyme, aquaporin 4, and anti-neuronal antibodies were negative. Serum immunoglobulin 4 levels were normal. The chest radiograph was normal. Digital subtraction cerebral angiography results were normal. Serum MOG antibodies were first tested using cell-based assays in 2018 and later during subsequent relapses and were found to be positive (1:10 dilution). Given the multiple relapses despite various immunotherapies (oral prednisolone, azathioprine, mycophenolate mofetil, rituximab, cyclophosphamide, and intravenous immunoglobulin), tocilizumab (400 mg monthly once) was initiated. The EDSS after 4 months of therapy was 5.5.

Nine cases of MOGAD with cranial nerve involvement apart from the optic nerve have been published.[3-8] Clinical and radiological features are shown in Table 1. Chart review revealed these findings: the mean age was 39.2 years (range 2–76); five were females; 12 episodes with cranial nerve involvement were recorded; clinical syndrome was brain stem syndrome (7), isolated cranial neuritis (2), encephalitis (1) and myeloradiculopathy (1), and asymptomatic (1); the most common clinically involved cranial nerves were the VII/VIII and V nerves (5), III (2), and XII (1) nerve; radiological isolated involvement was noted in V and III nerves.

Various postulations explain cranial nerve involvement other than the optic nerve. First, we assumed involvement of the root entry zone (REZ). Unlike the olfactory and optic nerves, which are exclusively composed of CNS-originated myelin, other cranial nerves derive myelin from oligodendroglia and Schwann cells. The REZ is the cisternal portion of the cranial nerve, which is covered by central myelin.[9] Antibody-mediated inflammatory destruction of the central myelin in the REZ is the most logical explanation for cranial nerve involvement. A similar mechanism has been proposed for cranial nerve involvement in NMOSD

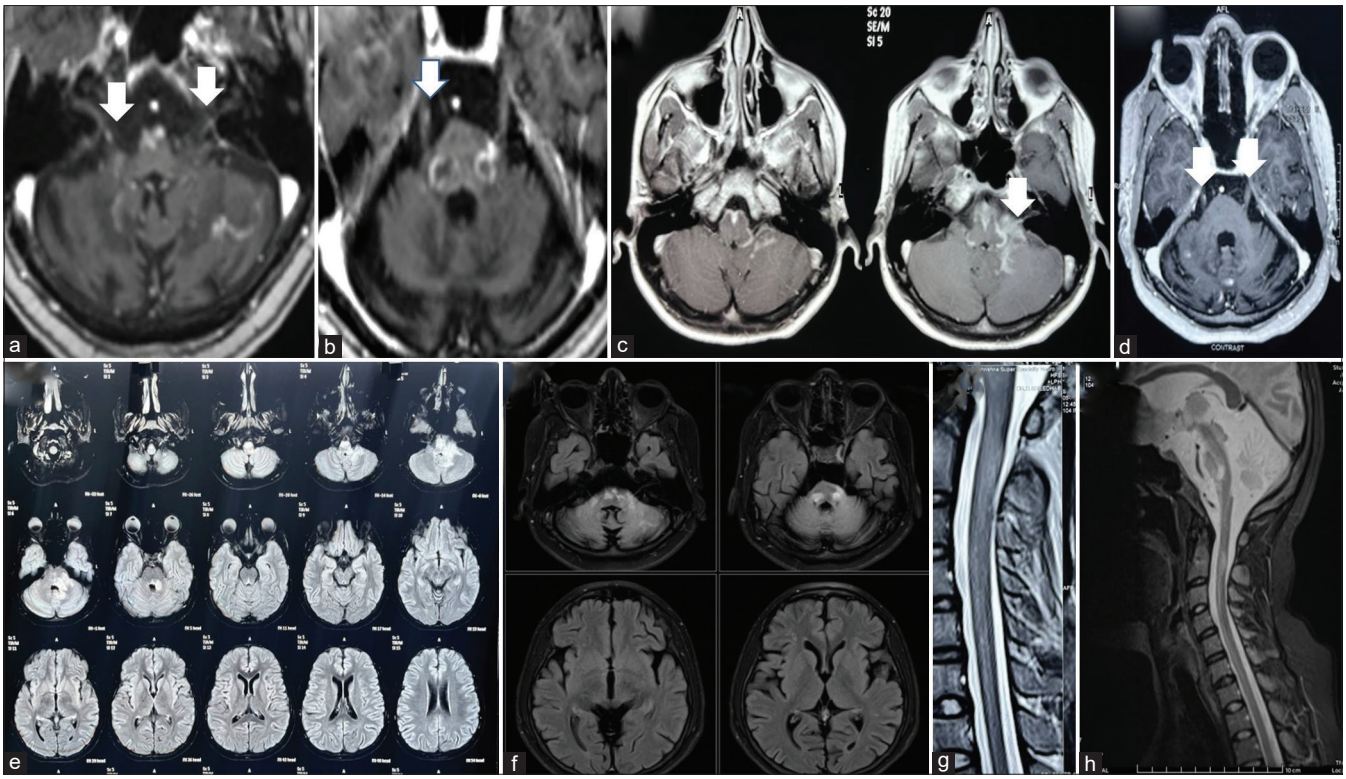

Figure 1: T1-weighted contrast MR axial sequences showing cranial nerve enhancement (bold white arrows): cisternal and intra-canalicular segments of bilateral VII-VIII complex (a) and cisternal segment of right V (b); cisternal VII-VIII on left side (c); cisternal segments of bilateral trigeminal (d); FLAIR axial of the brain showing hyperintensities in the medulla, pons, bilateral inferior cerebellar peduncles, left middle cerebellar peduncle, left cerebellum, and periaqueductal gray matter of midbrain (e and f); FLAIR sagittal of the cervical cord showing hyperintensities in central cervical cord up to C3 level (g); FLAIR sagittal of the brain and cervical cord showing cord atrophy and patchy hyperintensities in the pons and cervical cord (h)

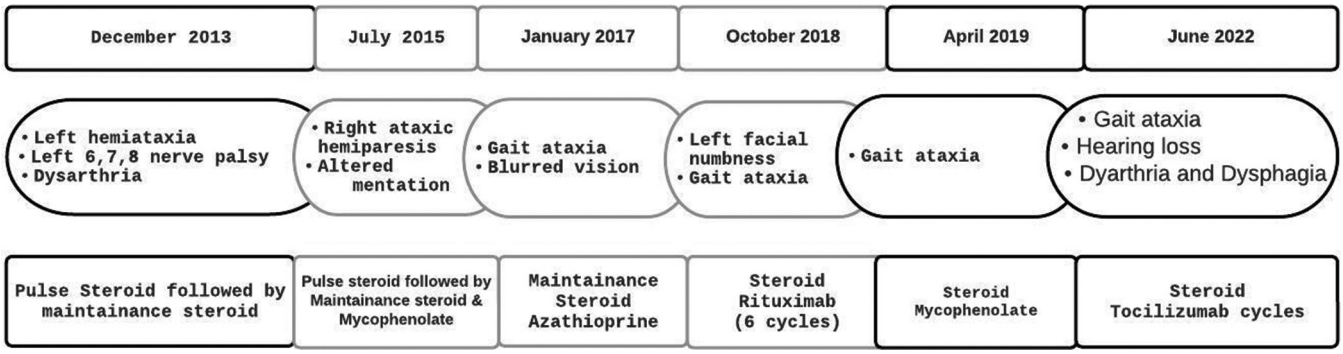

Figure 2: Line diagram showing disease course and relapses with episodes involving cranial nerves marked in black

and MS.[10,11] Cobo-Calvo *et al*.[3] attempted to demonstrate whether such cross-reactivity exists in sera from patients with MOGAD and non-human primates. However, the heterogeneity of MOG epitopes in humans and non-human primates has led to a negative result in that study. The length, volume, and depth of central myelin could vary across the cranial nerves. The mean (range) length (in millimeters) of the REZ was 10 (6–15) for VIII, 2.05 (0.5–4.0) for VII, 3.57 (2–6) for the sensory root of V, and 1.88 (1–4) for III. The volume of the central myelin was the highest in nerves V and VII.[12] This anatomical evidence supports the selective involvement of nerves III/V/VII/VIII in the present series. Of these, VIII nerve involvement is peculiar and reported exceedingly rarely in CNS inflammatory disorders.[13] All but one patient had brainstem inflammation in the series. This disease pattern reinforces the second assumption that cranial nerve involvement results from point-to-point extension of the inflammatory reaction from intra-axial brainstem pathologies. This spread, in turn, could be a mechanical progression of edema along the cranial nerves or propagation of inflammation along the venous structures adjacent to the cranial nerves.[11] However, despite significant intra-axial disease in the medulla and midbrain, IX-XII and III/IV were not involved in a few attacks. These findings further support the first hypothesis that these nerves have a lower volume of central myelin and any other mechanism,

Table 1: Clinical and radiological features of the reported cases

Author/ Year	Age (in years)/ Gender	Comorbidities	Disease duration	Episode Tally (Total episodes/Episodes with Cranial nerve Involvement)	Episode with Cranial nerve involvement	Clinical Syndrome	Clinically involved Cranial nerves
Du, Y *et al*., 2022[4]	64 Male	Gastric Ulcer	13 days	1/1	I	Polyneuritis cranialis	Left III Right V, VII Bilateral XII
Razali AM *et al*. 2020[5]	51 Female	None	12 years	Not available	I	Polyneuritis cranialis	Right III-VI
Cobo Calvo *et al*. 2019[3]	76 Male	Hypertension Dyslipidemia	2 years	1/2	I	Brain stem	Trigeminal (left)
					II	Nil	None
Cobo Calvo *et al*. 2019[3]	16 Female	Idiopathic congenital nystagmus	2 years	2/1	I	Encephalitis	None
Cobo Calvo *et al*. 2019[3]	52 Male	Hypertension Hypothyroid Chronic Kidney disease	1 year	1/1	I	Brainstem	Eight nerve
Kawakami S *et al*. 2019[6]	2 Female	None	4 months	1/1	I	Brainstem	Third nerve (Left)
Shen Y *et al*. 2018[7]	51 Female	None	1 month	1/1	I	Brainstem	Fifth and seventh (right)
Vazquez Do Campo R *et al*. 2018[8]	18 Male	None	21 days	1/1	I	Cranial neuritis and Myeloradiculopathy	Trigeminal (Right)
Our case	23 Female	Nil	8.5 years	6/3	I (Dec 2013)sw	Brainstem	Left VI-VIII
					II (April 2019)	Brainstem	None
					III (June 2022)	Brainstem	Right trigeminal and Bilateral eighth

Author/ Year	Radiologically Involved Cranial nerves	Other MRI Features (Brain)	Other MRI Features (Spine)	CSF findings Cell count (cells) Protein (mg/dl) Oligoclonal Bands (+/-)	Treatment
Du, Y *et al*., 2022[4]	None	T2/FLAIR hyperintensities in bilateral juxta cortical and periventricular white matter.	Not done	Normal	Pulse steroid and maintenance oral; Mycophenolate
Razali AM *et al*. 2020[5]	None	Normal	Not available	Not done	Pulse steroid and maintenance oral; Azathioprine
Cobo Calvo *et al*. 2019[3]	Trigeminal (left)	T2/FLAIR hyperintensities in bilateral superior cerebellar peduncle.	Not available	Normal 52 absent	None
	Trigeminal (right)	Not available	Not available	Not available	None
Cobo Calvo *et al*. 2019[3]	Bilateral third	FLAIR bilateral juxta cortical and supratentorial white matter hyperintensities.	Cervical T2 hyperintensity with enhancement on contrast	Normal	Antibiotics and Acyclovir
Cobo Calvo *et al*. 2019[3]	Bilateral trigeminal and vestibulocochlear	Asymmetrical FLAIR hyperintensities at the medulla oblongata and pons and in the dorsal pontine tegmentum.	Normal	27 51 Negative	Pulse steroid
Kawakami *et al*. 2019[6]	Left third	Normal	Normal	3 31 Negative	Pulse steroid

Contd...

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Author/ Year	Radiologically Involved Cranial nerves	Other MRI Features (Brain)	Other MRI Features (Spine)	CSF findings Cell count (cells) Protein (mg/dl) Oligoclonal Bands (+/-)	Treatment
Shen Y *et al*. 2018[7]	Root entry zone of bilateral trigeminal	T2/FLAIR hyperintense lesions involving the dorsal medulla (including area postrema), both MCP and aqueduct of midbrain.	Not available	78 47 Negative	Pulse steroid
Vazquez Do Campo R *et al*. 2018[8]	Root entry zone of right trigeminal	T2/FLAIR hyperintensities with patchy contrast enhancement in right hemi pons, middle cerebellar peduncle, left parietal region, and subcortical white matter of both cerebral hemispheres.	T2/FLAR hyperintensities with contrast enhancement in cervical spine, thoracic spine, and conus medullaris and lumbosacral roots	20 80 Present	Pulse steroid
Our case	Cisternal segment of left VII, VIII	T2/FLAR hyperintensities in medulla, pons, bilateral inferior cerebellar peduncles, left MCP, left cerebellum, periaqueductal gray matter of midbrain	Normal	8 71 Negative	Pulse steroid and maintenance oral prednisolone
	Cisternal segment of bilateral trigeminal	T2/FLAIR patchy hyperintensities in medulla, bilateral MCP, bilateral cerebellar hemispheres, right hemipons with focal enhancement on contrast	Not done	Not done	Pulse steroid and Mycophenolate
	Cisternal and intracanalicular segments of bilateral VII-VIII nerves and cisternal segment of bilateral trigeminal	T2/FLAIR patchy hyperintensities in the brainstem, bilateral MCP, and confluent hyperintensities in cerebellar white matter with patchy enhancement on contrast.	T2 hyperintensity in the cervical cord	3 52 Negative	Pulse steroid and monthly Tocilizumab

such as the existence of other specific antibodies different from MOG-antibody or an unknown demyelinating process specifically targeting the peripheral nerve.[3] One or all three mechanisms could cause cranial neuritis apart from the optic nerve in MOGAD. In the present series, we also noted that cranial nerves are often seen to show enhancement on MRI but with no evident symptoms. This subclinical MRI finding is akin to a radiologically isolated syndrome in MS. Such a clinico-radiological paradox is likely to be due to the involvement of clinically silent areas, low severity of inflammation, or co-existence of some pathological and biological factors that can cause the disease to manifest.[14]

In conclusion, cranial nerve involvement other than the optic nerve is rare in MOGAD but is often seen in brainstem encephalitis and is clinically silent. One or more putative mechanisms might play a role in this process.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

Y. Muralidhar Reddy, Subhendu Parida, Amreen Khan, Abhinay K. Gattu, Shyam K. Jaiswal, Jagarlapudi M. K. Murthy

Department of Neurology, CARE Institute of Neurosciences, CARE Hospital, Hyderabad, Telangana, India

Address for correspondence: Dr. Y. Muralidhar Reddy, Consultant Neurologist, CARE Institute of Neurosciences, CARE Hospital, Hyderabad, Telangana, India.
E-mail: muralidharnims@gmail.com

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