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LETTER TO THE EDITORS

Anti-MOG associated disease with intracranial hypertension after COVID-19 vaccination

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Abbreviations

FLAIR	Fluid attenuated inversion recovery
OD	Oculus dexter
OS	Oculus sinister

Dear Sirs,

Anti-myelin oligodendrocyte glycoprotein (MOG) antibodies, which target a glial protein on the myelin sheath, have recently been described as a new auto-immune signature of inflammatory demyelinating diseases that might involve optic neuritis, extended or short medullar lesions, and encephalic inflammatory lesions [1]. However, intracranial hypertension (ICH) has not been well described as a symptom of MOG antibody disease (MOGAD).

The spread of the COVID-19 pandemic implied an accelerated vaccination scheme with a great number of subjects vaccinated in a short period of time. This raises notifications of various manifestations that could be considered as vaccine side-effects. Some reports have mentioned acute disseminated encephalomyelitis (ADEM)-like manifestations [2, 3], and to date six cases of MOGAD after COVID-19 vaccination were notified [4–6].

A 35-year-old female patient with no prior medical history received one dose of ChAdOx1 nCoV-19 vaccine in March 2021. At week one after vaccination, she developed abdominal pain, nausea and headaches. Abdominal and ophthalmological explorations were normal. A brain MRI at week 4 showed white matter hypersignals of the area postrema, the cerebral peduncle and the left thalamus. Between week 4 and 5 from vaccination, she subsequently presented acute urinary retention that regressed spontaneously. Six weeks after the vaccine injection, she was hospitalized for confusion. Brain imaging found new lesions of the corpus callosum, the right optic radiation, the pons, and subcortical frontal left white matter, without gadolinium enhancement. It also revealed evidence for ICH, with enlarged optic nerves sheaths, lateral sinus stenosis and empty sella syndrome. An asymmetric papilledema with normal visual acuity was found upon ophthalmological examination. MRI and ophthalmological data are available in Fig. 1. CSF examination revealed meningitis (189 cells/µL with 64% of lymphocytes), and detectable oligoclonal bands. The opening pressure was 31 cmH_2O, before depleting 7 mL of CSF. There were no predisposing factors for idiopathic intracranial hypertension (normal body mass index, no concomitant treatment). Anti-MOG antibodies were positive in both serum and CSF (cytometric based array system from Euroimmun, confirmed by live-cell based assay from the French national reference laboratory in Lyon University hospital). An exhaustive workup ruled out other etiologies such as lymphoma, tuberculosis, auto-immune or other infectious diseases. Headaches and nausea disappeared after introduction of acetazolamide. Spinal cord MRI identified a 10 mm cervical lesion, without gadolinium enhancement.

Given the absence of activity signs on the MRI, the clinical improvement and the delay from the episode of urinary retention, the patient was discharged without steroids or immunosuppressive agents. Five months after the onset of symptoms, an MRI found regression of the inflammatory lesions and ICH signs, and disappearance of the medullar lesion without atrophy. There was no papilledema or visual field defect.

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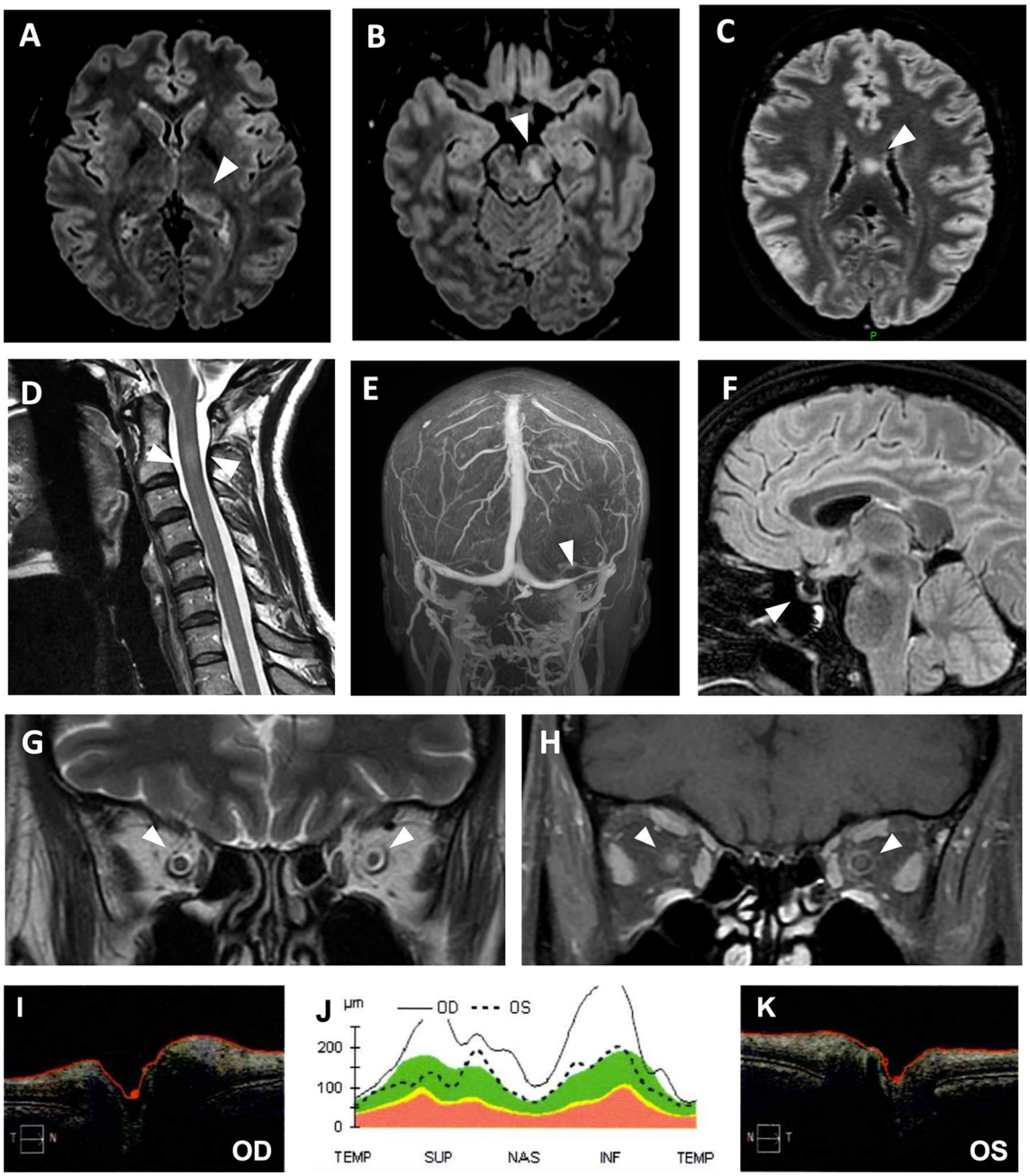

Fig. 1 MRI and optical coherence tomography data. **A–B** Data from the first MRI showing white-matter FLAIR hyperintensities of the left posterior thalamus (panel A), left cerebral peduncle (panel B) (arrow heads). C–D Second MRI data showing white-matter FLAIR hyperintensities of the corpus callosum (panel C), and C2 myelitis (in T2-weighted images, panel D) (arrow heads). **E–G** Intracranial hypertension aspects with right lateral sinus stenosis (panel E), empty sella syndrome (panel F), and enlarged optic nerves sheaths (panel G) (arrow heads). **H** Neuritis and perineuritis of the optic nerves in T1-weighted post gadolinium sequences during the relapse as optic neuritis. (arrow heads). **I** and **K** horizontal tomography of the papilla for both eyes showing papilledema. **J** Optical coherence tomography data for the thickness of the retinal nerve fiber layer (normal distribution in green) showing increased thickness for both eyes

Six months after the onset of symptoms, the patient presented decreased visual acuity at 9/10th and headaches despite increased acetazolamide doses. A new MRI identified a right optic neuritis with bilateral optic perineuritis (Fig. 1H). Anti-MOG antibodies were still detectable. She was treated with 3 methylprednisolone pulses and azathioprine was introduced as a maintenance therapy; five months later, no relapse was observed.

We report a case of newly diagnosed MOGAD with intracranial hypertension revealed after SARS-CoV-2

vaccination. MOGAD is mostly characterized by optic neuritis, followed by myelitis [7], but few associations with ICH have been reported to date [8]. In a retrospective study of 87 MOGAD patients, 18 (21%) presented with encephalitis, among which 7 (41%) had ICH [9]. Of the 5 patients with anti-AQP4 positivity of the cohort, none had ICH. A recent retrospective cohort found that optic disc edema was more frequently found in anti-MOG optic neuritis than with anti-AQP4 (45.5 vs 7%, $p = 0.006$). This study also reported ICH in one patient with MOGAD [10]. Papilledema can be caused by both ICH and anterior optic neuritis itself, which makes differential diagnosis difficult. In spite of a few reported cases, description of ICH in MOGAD remains rare. A prospective series studying serum samples from 34 patients presenting with idiopathic ICH found no anti-MOG positivity [11]. The link between intracranial hypertension and anti-MOG positivity is unclear, since these auto-antibodies do not target structures involved in the circulation of the CSF. However, auto-immunity and inflammation might have indirect roles in the accumulation of CSF within the ventricular system, as suggested by a series of serum samples from patient with idiopathic intracranial hypertension, where IgG reacted with membrane antigens of rat hippocampal and cortical neurons [10]. Systematic measurement of CSF opening pressure might reveal more cases of elevated values in MOGAD.

To our knowledge, this is the first case of relapsing MOGAD reported after COVID-19 vaccination. Indeed, one case of extensive myelitis and encephalitic lesions with anti-MOG antibodies, resolutive after methylprednisolone, has been reported after ChAdOx1 nCoV-19 vaccine, defining a monophasic ADEM-like presentation [4]. A recent report accounted for an inaugural longitudinal extensive transverse myelitis after the same vaccine [5].

Debate is still ongoing about MOGAD triggering by infectious agents. The MOGADOR study found 20% of patients presenting infection within 1 month before the disease onset [7]. A case of anti-MOG encephalitis following severe SARS-CoV-2 infection has been described in a 13-month-old child, where evolution was favorable with steroids [12]. Cases of ADEM and encephalitis following ChAdOx1 nCoV-19 vaccine have also been notified without anti-MOG positivity [2, 3]. The pharmacovigilance unit analyzed reporting of MOGAD then NMOSD in VigiBase, the World Health Organization's (WHO) global database of suspected adverse reactions to medicinal products, developed and maintained by Uppsala Monitoring Centre (UMC). The search was made using the Preferred Term (PT) "myelin oligodendrocyte glycoprotein antibody-associated disease" and "neuromyelitis optica spectrum disorder" in the Medical Dictionary for Regulatory Activities (MedDRA) and with ChAdOx1 nCoV-19 vaccine (request made on February 24th, 2022). In Vigibase, the information comes from various sources, the probability for the suspected adverse effect to be drug-related depends on the case. The information does not represent the opinion of the UMC or the WHO. Of the 15 cases of MOGAD registered after COVID-19 vaccines, only one was reported with ChAdOx1 nCoV-19 vaccine, in a 43-year-old woman, 9 days after the last dose of vaccine. To date, 17 cases of newly diagnosed NMOSD have been declared after ChAdOx1 nCoV-19 vaccine, where the vaccine was the only suspected drug. Eleven cases occurred in women [median age of 56 years, interquartile range (IQR) 40–66], with no fatal case. The median time between the last dose of vaccine and the adverse event was 19 days (IQR 8.5–27; n available = 11). Four cases were considered as "recovering" or "recovered with sequelae"; seven were "not recovered", six outcomes were "unknown".

So far, ChAdOx1 nCoV-19 vaccine is not significantly associated with MOGAD or NMOSD. Then, we strongly recommend COVID-19 vaccination in all patients, considering this data and the crucial need for a population-wide vaccinal protection to halt a worldwide pandemic that has now been evolving for two years.

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Declarations

Conflicts of interest The authors declare that there is no conflict of interest.

Informed consent The patient provided written informed consent for the publication of this report.

Ethical approval Data was collected and managed in accordance with the CARE statement checklist (https://www.care-statement.org/checklist). This study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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