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LETTER TO THE EDITORS

Combined central and peripheral demyelination after COVID-19 vaccination

Pedro Coelho[1] · André Paula[1] · Isabel Vidal Martins[1] · Catarina Falcão de Campos[1,2] · João Ferreira[1,2] · Ana Patrícia Antunes[1,2] · Luísa Albuquerque[1,2]

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Dear Sirs,

Combined central and peripheral demyelination (CCPD) is a rare neurological entity that affects both the central and peripheral nervous system with demyelinating lesions [1, 2]. The pattern of involvement of the central nervous system (CNS) includes frequent bilateral optical neuritis, involvement of grey matter and occasional longitudinally extensive transverse myelitis (LETM) in the absence of oligoclonal bands (OCB) or antibodies such as antiaquaporin-4 (AQP4) and anti-myelin oligodendrocyte glycoprotein (MOG) [3]. Peripheral nervous system (PNS) involvement occurs mainly as a chronic inflammatory demyelinating polyneuropathy (CIDP)-like disease [3]. Infections and vaccinations are known triggers [1]. CCPD typically evolves aggressively with progressive cumulative neurological impairment despite immunosuppression [1].

A 48-year-old man with previous essential arterial hypertension medicated with irbesartan, hydrochlorothiazide and lercanidipine, developed anosmia, ageusia, lower limb weakness (noticed by the patient as an increased difficulty to perform his daily exercise routine), and an irregular bowel pattern, 3 weeks after administration of COVID-19 vaccine (AstraZeneca®- ChAdOx1). A COVID-19 infection was excluded by two negative SARS-CoV-2 RT-PCR tests. Most complaints remitted spontaneously in 5 days, except for lower limb weakness. Twelve weeks after the first administration, the patient received the second dose of AstraZeneca®-ChAdOx1 vaccine. Five days later, he developed bilateral lower limb numbness, gait instability, band-like pain at mid-thoracic level and urinary dysfunction, that progressed over 3 weeks. There were no recent travels to foreign countries, introduction of new medication or exposure to toxics. There were no previously known neurological or autoimmune diseases in the patient's family.

The patient was then admitted and neurological examination disclosed hypoesthesia with a T6 sensory level, but also a more marked stocking pattern hypoesthesia in lower limbs, a distal proprioception defect, mixed ataxia in the lower limbs and gait ataxia, weakened lower limb osteotendinous reflexes and extensor plantar responses. There were no cranial nerve abnormalities including bedside evaluation of visual acuity, campimetry and fundoscopy. The general examination was unremarkable. An incomplete thoracic transverse myelitis diagnosis was assumed. Spinal cord MRI showed multiple small cervical, thoracic and lumbar T2 hyperintense lesions, without contrast enhancement (Fig. 1).

The initial inpatient investigation focused on ancillary studies directed to CNS inflammatory and demyelinating disorders. Brain MRI was unremarkable, and visual-evoked potentials were normal. No other specific optic pathway studies were performed such as OCT and optic nerve dedicated sequences on MRI. Laboratory studies including systemic autoimmune, infectious, metabolic, and granulomatous work-up were negative or within normal ranges (Table 1). Fixed cell-based immunofluorescence assays (CBA) for AQ4-IgG and MOG-IgG antibodies were negative. Recent infection with COVID-19 was once again excluded through negative nasal and pharyngeal polymerase chain reaction (PCR) swabs. Anti-SARS-CoV-2 antibodies were positive with a titter of 863.0 U/mL. Cerebrospinal fluid (CSF) analysis revealed 247 mg/dL proteins, 0.8 cells and normal glycorrhachia and negative OCB, CSF cultures and serologies.

✉ Pedro Coelho
peminco@gmail.com

[1] Serviço de Neurologia, Departamento de Neurociências e Saúde Mental, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Avenida Professor Egas Moniz, 1649-035 Lisbon, Portugal

[2] Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal

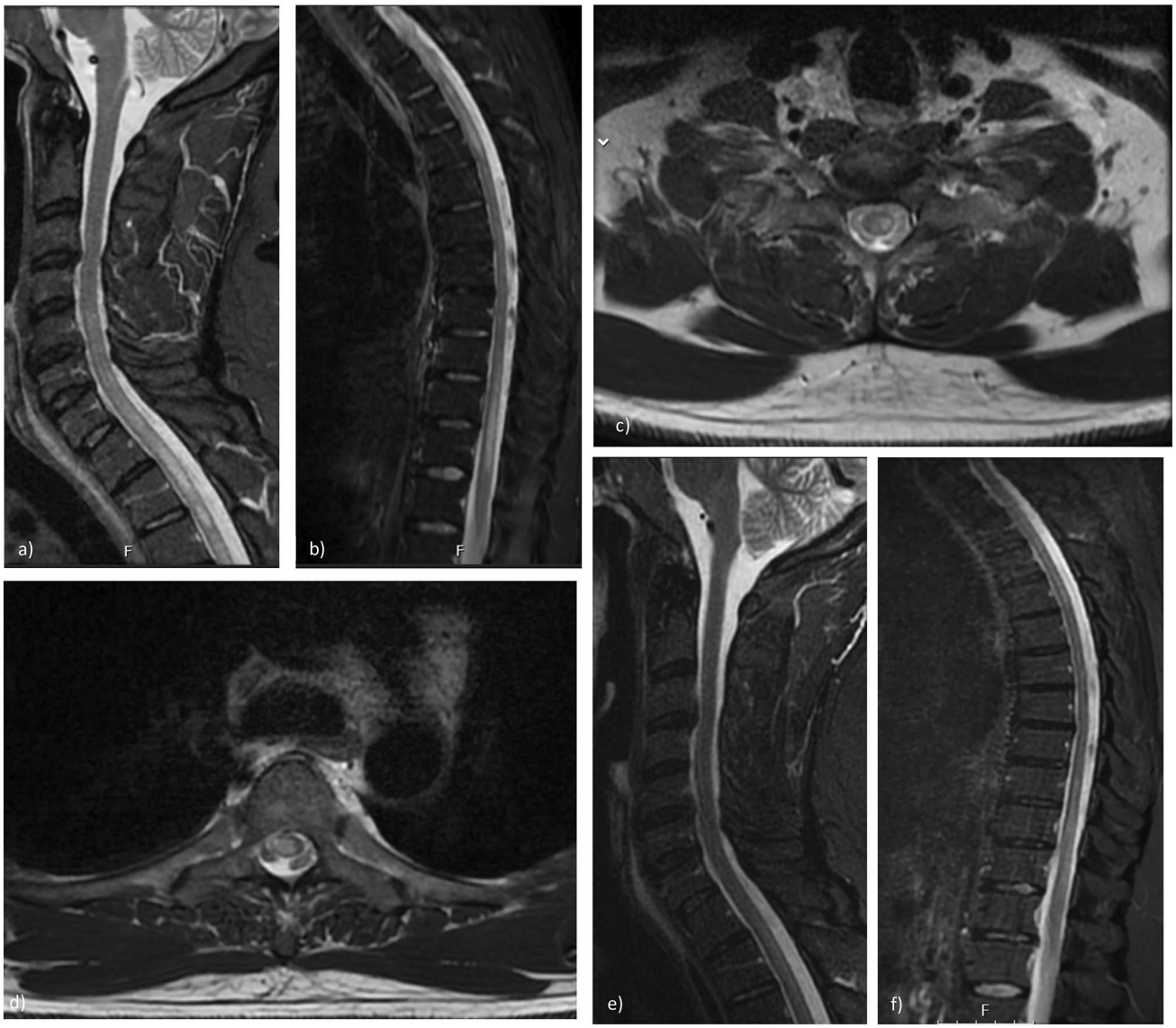

Fig. 1 **a**, **b** Spinal cord lesions identified at C7, C7-Th1, Th5-Th6 and Th11-Th12 levels (T2-STIR sequence); none of the lesions presented gadolinium enhancement; **c**, **d** spinal cord lesion at C7 level and at D4 level in an axial view (T2-sequence sequence); **e**, **f** improvement of the lesions previously identified on the follow-up MRI at 4 months

Additionally, an EMG was performed, which showed a demyelinating sensorimotor polyneuropathy characterized by prolonged motor distal latencies, reduced motor and sensory nerve conduction velocities and increase F-wave latencies in multiple nerves in both upper and lower limbs (Supplemental Table 1), suggestive of CIDP.

A final diagnosis of CCPD was made. Intravenous methylprednisolone 1 g/day was administered during 5 days, followed by oral prednisolone 1 mg/kg/day (total 80 mg/day). Sensitive abnormalities, lower limb ataxia and ambulatory ability were improved within 1 week of corticosteroids treatment.

In addition, further laboratory work-up excluded anti-MAG, anti-gangliosides (GM1, GD1a, GD1b, GQ1b), anti-sulfatides, anti-contactin 1, anti-neurofascin 140, 155 and 186 disorders.

At 8 months follow-up, oral prednisolone was tapered down to 10 mg/day and the patient currently remains free of clinical relapses and following a slow tapering plan. Spinal cord MRI re-evaluation at 4 months showed almost complete remission of the previous lesions. EMG re-evaluation at 7 months maintained the same neurophysiological findings.

Cases of CCPD following SARS-CoV-2 vaccination are very rare, based on the scarce number of reports in the subject [4, 5]. The association is supported by literature findings

Table 1 Summary of aetiology-oriented laboratory studies

Blood and serum	
Anti-ds-DNA	Negative
ANA screening	Negative
Anti-MPO and anti-PR3	Negative
Angiotensin converting enzyme	41 U/L (normal ≤ 51 U/L)
Anti-AQ4	Negative
Anti-contactin 1	Negative
Anti-gangliosides (GD1a, GD1b, GM1, GQ1b)	Negative
Anti-MAG	Negative
Anti-MOG	Negative
Anti-neurofascin 140, 155, 186	Negative
Anti-sulfatides	Negative
Erythrocyte sedimentation rate	10 mm/h
Anti-SARS-CoV-2 (S1-RBD Ig)	863.0 U/mL
HIV 1/2	Negative
HSV 1 and 2	IgM and IgG negative
VZV	IgM negative; IgG positive
CMV	IgM negative; IgG positive
EBV	IgM negative; IgG positive
HAV	IgM and IgG negative
anti-HBs	Positive
Anti-HCV	Negative
HEV	IgM and IgG negative
Borrelia burgdorferi	IgM and IgG negative
Interferon-gamma release assay	Negative
Treponema pallidum	Non-reactive
Cerebrospinal fluid	
Cells	0,8 cells (Normal < 5 cells)
Proteins	247.1 mg/dL (Normal < 45 mg/dL)
Glucose	68 mg/dL
Oligoclonal bands (OCB)	Absent
Cultures (bacterial)	Negative
Treponema pallidum (VDRL)	Non-reactive
Borrelia burgdorferi	Negative
Neurotropic viruses PCR array*	Negative

ANA antinuclear antibodies, *AQP4* Aquaporin-4, *CMV* cytomegalovirus, *EBV* Epstein–Barr virus, *HAV* Hepatitis A virus, *HBs* Hepatitis B surface antigen, *HCV* Hepatitis C virus, *HEV* Hepatitis E virus, *HIV* human immunodeficiency virus, *HSV* herpes simplex virus, *MAG* myelin associated glycoprotein, *MOG* myelin oligodendrocyte glycoprotein, *PCR* polymerase chain reaction, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *VZV* varicella zoster virus

*HSV1, HSV2, CMV, EBV, HHV6, HHV7, VZV, adenovirus, enterovirus and parechovirus

of CCPD development after infections or vaccines [1], strengthened in our case by the temporal relation between the first jab and first neurological complaints (3 weeks' timeframe), and the striking neurological aggravation starting within days of the second jab.

CCPD is a rare neurological condition which includes heterogeneous clinical presentations such as myeloradiculoneuropathy, encephalopathy, cranial neuropathy, length-dependent peripheral neuropathy or pseudo-Guillain–Barré syndrome and can present in acute, relapsing–remitting and chronic forms [1, 3]. One important issue regarding this entity is whether it is a single condition due to a common immunopathogenic mechanism or two coincidental demyelinating disorders (multiple sclerosis [MS] and CIDP), but the pattern of CNS involvement (atypical for MS) favours the former [3]. The pathophysiological mechanism in this disease is elusive, as it is not known if the same antigenic target occurs in both the PNS and CNS, or whether there is a cross-reactive immune response to an insult to either one [6]. In 2013, Kawamura et al. pointed the elevated frequency of anti-neurofascin antibodies in patients with CCPD [3]. Neurofascins are transmembrane adhesion molecules expressed at the nodes and paranodes of both the CNS and PNS [7]. Since then, there have been some case reports involving neurofascin-155 in CCPD [8–10]. However, there are also reports of CCPD without positive neurofascin-155 antibodies, such as our case, highlighting the complexity of finding potential epitopes [11].

Another possible target antigen is the peripheral myelin P1 protein expressed in peripheral nerves, which is identical to the myelin basic protein [12]. There have been cases of CCPD in the context of anti-MOG antibody-associated disorders [13, 14]. One of the pathophysiological explanations for the PNS involvement in these disorders is that secretion of a MOG isoform into the CSF and posterior drainage into the bloodstream could lead to a second autoimmune event through molecular mimicry with peripheral myelin proteins. [14].

There is extensive literature on the association between SARS-CoV-2 infection and the development of different types of CNS and PNS involvement, most of the times in the form of demyelinating conditions, including reported cases of LETM and optic neuritis associated with anti-MOG antibodies [15, 16]. The SARS-CoV-2 spike protein can bind to sialic acid-containing glycoprotein and gangliosides on cell surfaces and this could drive an antibody cross-reactivity response and explain the neurological injury [17].

Several vaccines are also rare potential triggers for demyelination of CNS or PNS, namely in ADEM or Guillain–Barré syndrome [18, 19].

The CCPD response to immunotherapy supports a dysimmune mechanism [1, 2]. In a cohort study by Cortese et al. including 31 patients, 65% of them developed CCPD after infection or vaccination—2 cases after vaccination (influenza and *Streptococcus pneumoniae* vaccines, respectively) [1].

SARS-CoV-2 vaccination specifically has been related either to CNS or to PNS demyelination, including cases of

transverse myelitis, MS-like, ADEM-like, and NMOSD-like presentations, AIDP and CIDP [17, 18].

There has been two case reports of CCPD following ChAdOx1 vaccination [4, 5]. One of the reports, like in our case, described a patient presenting 10 days after the first inoculation as a GBS, and whose brain and spinal MRI showed a short cervical spinal cord demyelinating lesion and multiple subcortical and periventricular lesions in the brain [4]. The clinical condition also improved with corticosteroid, and on a 3-month follow-up, there was a complete neurological recovery and remission of the MRI lesions. The other report consisted of a severe neurological presentation associated with anti-neurofascin 155 IgG which improved with corticosteroids and IvIG [5].

In our particular case, the neurological symptoms triggered after vaccination in both doses favours the relationship between this CCPD case and ChAdOx1 vaccine. The more severe manifestations after the second dose are in probable relation with an antibody-dependent enhancement mechanism, which has a theoretical higher risk of occurrence in inactivated viral and viral-vector-based vaccines and that also has been previously reported in various respiratory virus infections [22].

Although our case presents a benign evolution and CCPD is typically regarded as a disease with an aggressive course, there is still some clinical uncertainty and heterogeneity in this condition. In one of the biggest cohort studies [2], 65% of patients had no or mild disability after the acute phase, which is in contrast with the work of Cortese et al. [1], where 71% of patients had a poor outcome. The differences between both studies could be explained by demographics and paraclinical features [1]. Nevertheless, in both studies, there was a good response to treatment in the acute phase [1, 2]. Moreover, patients with simultaneous onset of peripheral and central disease are more likely to have a monophasic course and to have a better response to treatment, as in our case. [2]

Strikingly, in the Cortese et al. cohort study, the mean delay between inflammatory events in the relapse-remitting subgroup of patients was 12 months, which is longer than our follow-up time [1]. Both the relapse-remitting and the chronic progressive subgroups seem to have a poor response to treatment when there is disease recurrence [1].

This case of CCPD may be included in the spectrum of demyelination conditions reported following SARS-CoV-2 vaccination. Follow-up evaluation will be important to understand if these particular cases will be monophasic demyelinating events, or the first event of a relapsing–remitting or chronic condition.

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Declarations

Conflicts of interest The author declares that they have no conflict of interest.

Ethical standards The authors declare that they complied with ethical standards and the patient gave written informed consent for the publication of this report.

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