The Canadian Journal of Neurological Sciences (2023), **50**, 141–143
doi:10.1017/cjn.2021.256

Canadian Journal of Neurological Sciences
Journal Canadien des Sciences Neurologiques

Letter to the Editor: New Observation

Combined Central and Peripheral Demyelination with Anti-Neurofascin155 IgG Following COVID-19 Vaccination

Eleonora Matteo[1], Michele Romoli[2,3], Calogero Calabrò[1], Laura Piccolo[2], Tiziana Lazzarotto[4,5], Manuela Suserea[2], Sara Contardi[2], Silvia Stagni[6], Liliana Gabrielli[5], Stefano Forlivesi[2], Mirna Bassi[7], Morena Borsari[8], Chiara Sacripanti[8], Elena Merli[2], Federica Naldi[2], Keivan M. Kaveh[2], Annamaria Borghi[2], Elisabetta Magni[9], Luigi Simonetti[6], Carlo Descovich[10], Elisa Vegezzi[11], Matteo Gastaldi[12] and Andrea Zini[2]

[1]Department of Biomedical and Neuromotor Sciences, Alma Mater-University of Bologna, Bologna, Italy, [2]IRCCS Istituto delle Scienze Neurologiche di Bologna, Department of Neurology and Stroke Center, Maggiore Hospital, Bologna, Italy, [3]Neurology and Stroke Unit, "Bufalini" Hospital, Cesena, Italy, [4]Microbiology Unit, IRCCS St. Orsola Polyclinic, Bologna, Italy, [5]Department of Experimental, Diagnostic and Specialty Medicine, IRCCS S. Orsola Polyclinic, Alma Mater-University of Bologna, Bologna, Italy, [6]IRCCS Istituto delle Scienze Neurologiche di Bologna, Neuroradiology Unit, Maggiore Hospital, Bologna, Italy, [7]LUM Metropolitan Laboratory, Maggiore Hospital, AUSL Bologna, Bologna, Italy, [8]Pharmaceutical Department, AUSL Bologna, Bologna, Italy, [9]IRCCS Istituto delle Scienze Neurologiche di Bologna, Neurorehabilitation Unit, Maggiore Hospital, Bologna, Italy, [10]Department of Clinical Governance and Quality, AUSL Bologna, Bologna, Italy, [11]Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy and [12]Laboratory of Neuroimmunology, IRCCS National Neurological Institute C. Mondino Foundation, Pavia, Italy

Keywords: COVID-19; Demyelination; CNS inflammation; Neuroimmunology; Peripheral neuropathy

Combined central and peripheral demyelination (CCPD) is a rare demyelinating process that involves both the central and peripheral nervous system and can occur after infection or vaccination.[1] Here we describe the case of a patient that developed CCPD after having received the first dose of ChAdOx1 nCoV-19 vaccine.

A 52-year-old man with no significant comorbidities presented to the ER reporting sudden-onset tingling paresthesia in his fingers and toes, and reduced hand dexterity. Three weeks earlier, a COVID-19 outbreak had occurred in the penitentiary where he worked. Eleven days before admission, he was vaccinated with ChAdOx1 nCoV-19. At admission, the neurological examination showed VII cranial nerve deficit, dysarthria, and bilateral hand intrinsic muscles deficit (MRC = 4/5), normal deep tendon reflexes, and a slightly ataxic gait. Head and chest CT scan and blood exams were unremarkable. He was admitted to the Neurology Unit (Day 0). On Day 2, sensory disturbances worsened, reflexes became diffusely weak, and cranial nerves involvement became prominent with diplopia, perioral paresthesia, bilateral facial diplegia, dysphagia, hypophonia, and severe dysarthria. Cerebrospinal fluid (CSF) and brain magnetic resonance imaging (MRI) were unremarkable. Spine MRI revealed contrast enhancement of cauda equina roots (Figure 1A); electromyography showed a severe, distally predominant demyelinating polyradiculoneuropathy. He was started on intravenous immunoglobulin (IVIg), 0.4 g/kg for 5 days (days 3–7). On Day 4, hypercapnic respiratory failure required oxygen support in the intensive care unit. Three days after IVIg start, he started to improve, and on Day 8, he was transferred to the Neurology Unit. On Day 11, he was weaned off oxygen via nasal cannula and started rehabilitation (Figure 2 for clinical course). On Day 17, the patient reported blurred vision, especially in the right eye; three days later, he noted hypophonia and fatigability during speech. An ophthalmoscopic exam revealed bilateral optic papillitis; visual acuity was 8/10 right and 9/10 left. Visual evoked potentials showed bilateral slow conduction with right mild amplitude reduction. A second IVIg cycle did not provide substantial benefit. On day 28, brain MRI revealed contrast-enhancing multifocal bilateral demyelinating lesions (Figure 1B–G). After 5 days of high-dose intravenous corticosteroids (1g die, Days 30–34), the patient completely recovered, and he was discharged with oral prednisone. After 2 months, he is clinically stable.

CSF examination on day 1 showed normal proteins and white blood cell count; cytoalbuminologic dissociation emerged on days 7 and 19.

Electromyography on day 1 showed severe, distally predominant, demyelinating symmetric polyradiculoneuropathy (DADS) with prolonged distal motor latency at lower limbs, diffuse reduction in nerve conduction velocity, absent F-waves in most of the explored nerves and increased temporal dispersion at lower limbs. On day 13 neurophysiological studies showed a slight worsening.

Serum and CSF IL-6 and IL-8 cytokines peaked during the first disease stage, decreasing thereafter (Figure 2). Anti-spike antibodies progressively raised over time. Serum samples tested positive for anti-NF155 IgG autoantibodies and negative for anti-contactin-1, and anti-CNTN-1/CASPR-1 complex. IgG isotype determination is ongoing.

Corresponding author:: Andrea Zini, IRCCS Istituto delle Scienze Neurologiche di Bologna, Department of Neurology and Stroke Center, Maggiore Hospital, Largo Nigrisoli 2, 40133 Bologna, Italy. Email: a.zini@ausl.bologna.it

Cite this article: Matteo E, Romoli M, Calabrò C, Piccolo L, Lazzarotto T, Suserea M, Contardi S, Stagni S, Gabrielli L, Forlivesi S, Bassi M, Borsari M, Sacripanti C, Merli E, Naldi F, Kaveh KM, Borghi A, Magni E, Simonetti L, Descovich C, Vegezzi E, Gastaldi M, and Zini A. (2023) Combined Central and Peripheral Demyelination with Anti-Neurofascin155 IgG Following COVID-19 Vaccination. *The Canadian Journal of Neurological Sciences* **50**: 141–143, https://doi.org/10.1017/cjn.2021.256

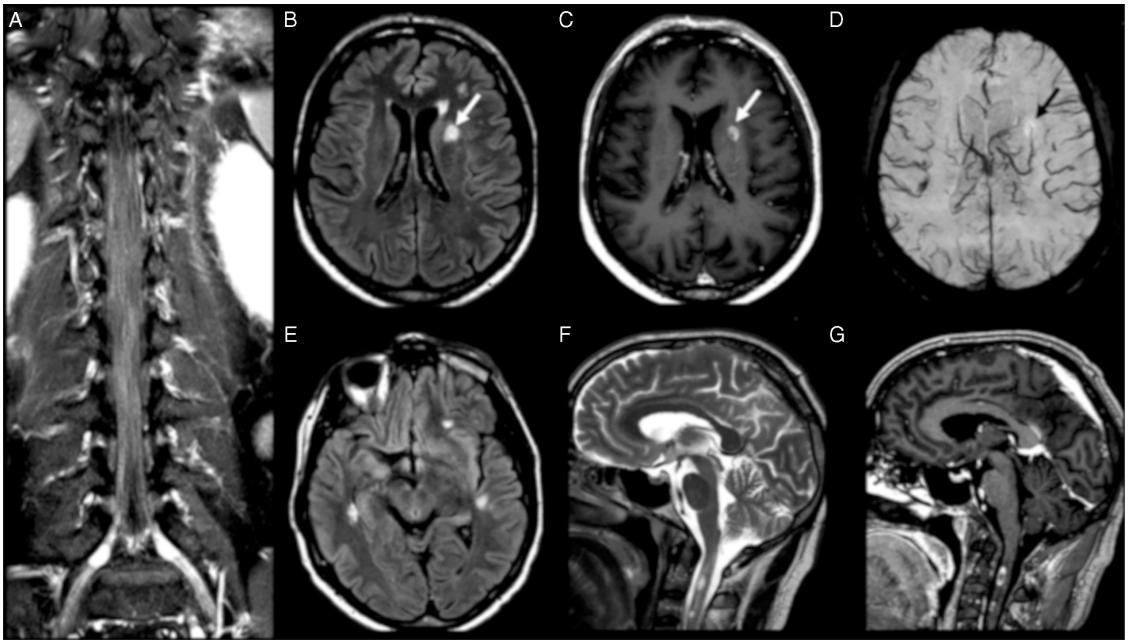

Figure 1: Coronal T1 SPIR image of lumbar spine after gadolinium injection showing contrast enhancement of cauda equina nerve roots (A); axial FLAIR (B), post-contrast SE T1 (C) and SWI (D) sequences showing a contrast-enhancing, T2-hyperintense perivenular lesion (arrows); oblique axial FLAIR image showing multiple subcortical and periventricular white matter lesions (D); sagittal TSE T2 (E) and T1 post-contrast (F) sequences showing two T2-hyperintense and T1-hypointense, Gd-enhancing, cervical spine lesions.

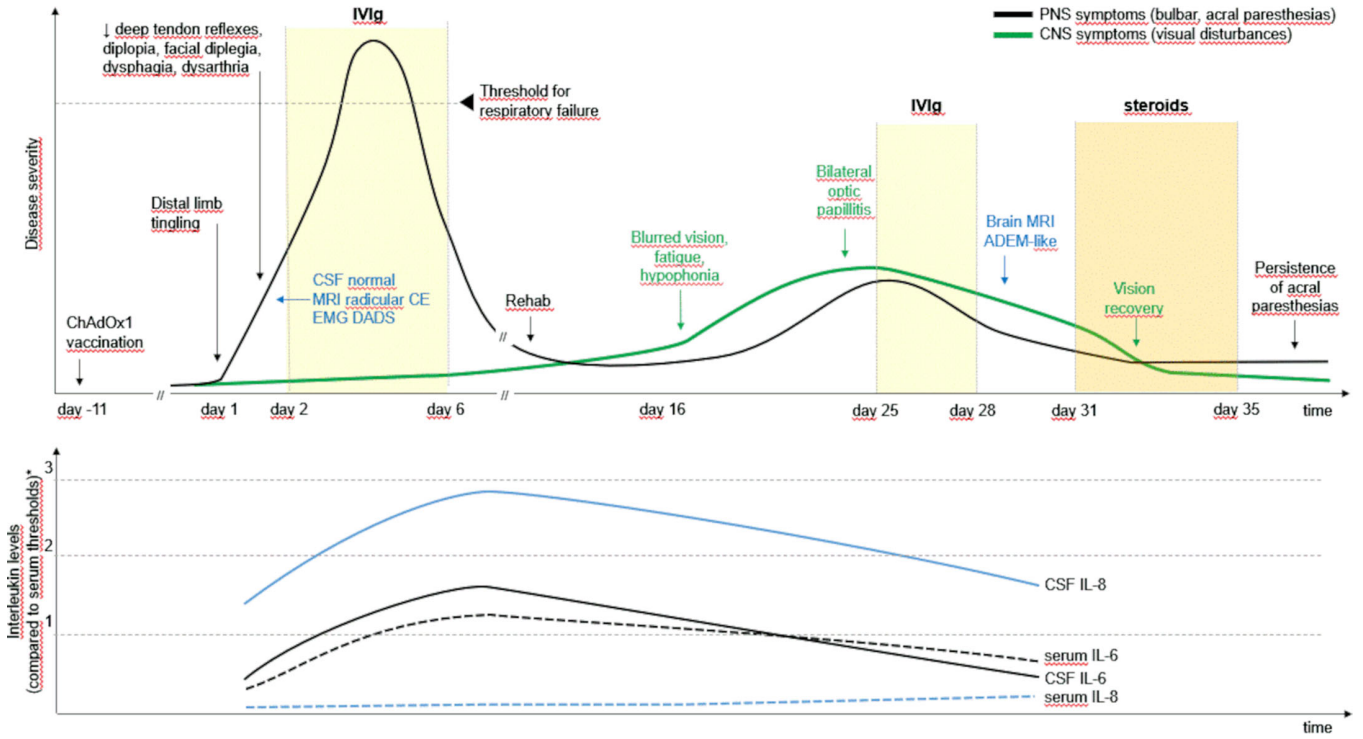

Figure 2: Above panel: clinical course and administered therapies; bottom panel: IL-6 and IL-8 levels in serum and CSF during hospital stay. *concentration of interleukins is displayed according to ratio with serum threshold for both serum and CSF. ADEM = acute demyelinating encephalomyelitis; CE = contrast enhancement; CSF = cerebrospinal fluid; CNS = central nervous system; DADS = distal acquired demyelinating symmetric neuropathy; EMG = electromyography and nerve conduction study; IL = interleukin; IVIg = intravenous immunoglobulin; PNS = peripheral nervous system.

Infectious and other autoimmune screening was negative (see Supplementary Material Table 1 for full lab diagnostics).

The rise of the anti-spike protein title demonstrates a mounting immune response against SARS-CoV-2, which might have triggered an autoimmune process. Such finding seems to replicate the mechanisms of autoimmune-mediated complications of vaccination[2] and is in accordance with data from a large CCPD case series, where recent vaccination/infection triggered two-thirds of cases.[1]

https://doi.org/10.1017/cjn.2021.256 Published online by Cambridge University Press

Peripheral nervous system (PNS) involvement can happen before, hand-in-hand with, or after central nervous system (CNS) involvement[1,3,4] and influences the first treatment choice, as those with early PNS involvement might receive IVIg/plasmapheresis rather than steroids.[1,4] CCPD has also been reported with anti-NF155 autoantibodies.[3,4] This case exhibits some of the characteristic features of CCPD with anti-NF155 antibodies: the MS-like CNS involvement, with perivenular inflammation at periventricular sites (Figure 1D); absence of oligoclonal bands in CSF; damage in nerve roots and DADS.[4]

An attempt to better characterize the patient's immune response has been made by measuring cytokines levels both on serum and on CSF across the stay. The rise in IL-8 CSF levels (several times higher than serum) could point to an intrathecal autoimmune process, diverging from the pathogenesis of Guillain-Barré syndrome related to antiparanodal antibodies, with no oligoclonal bands and normal IgG indices.[5]

The worldwide rollout of COVID-19 vaccines is eventually leading to the emergence of very rare syndromes after vaccination. Very rare events with unknown epidemiology are hardly interpretable in their relationship with vaccination. Here, although the temporal association of CCPD and vaccination does not prove any causal link, a connection with vaccine exposure must be considered, given the very rare nature of the syndrome and the negative findings emerging from all investigations.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/cjn.2021.256.

Conflict of Interest. None.

Statement of Authorship. AZ provided and cared for the study patient, acquired data, co-wrote the paper, revised and gave final approval to the manuscript, supervised the work; EM (Eleonora Matteo), CC, LP, MR: provided and cared for the study patient, acquired data, co-wrote the paper, revised and gave final approval to the manuscript; MS, SC: performed neurophysiology techniques, provided and cared for the study patient, revised and gave final approval to the manuscript; SS, LS: performed imaging diagnostic techniques, revised and gave final approval to the manuscript; TL, LG, MB, EV, MG: performed microbiological and/or immunological laboratory testing, revised and gave final approval to the manuscript; SF, EM (Elena Merli), FN, KK, AB: provided and cared for the study patient, revised, and gave final approval to the manuscript; MB, CS, CD: acquired data, revised and gave final approval to the manuscript.

References

1. Cortese A, Franciotta D, Alfonsi E, et al. Combined central and peripheral demyelination: clinical features, diagnostic findings, and treatment. J Neurol Sci. 2016;363:182–87. DOI 10.1016/j.jns.2016.02.022.
2. Scully M, Singh D, Lown R, et al. Pathologic antibodies to platelet factor 4 after ChAdOx1 nCoV-19 vaccination. N Engl J Med. 2021;384:2202–2211. DOI 10.1056/NEJMoa2105385.
3. Ogata H, Matsuse D, Yamasaki R, et al. A nationwide survey of combined central and peripheral demyelination in Japan. J Neurol Neurosurg Psychiatry. 2016;87:29–36. DOI 10.1136/jnnp-2014-309831.
4. Kira J, Yamasaki R, Ogata H. Anti-neurofascin autoantibody and demyelination. Neurochem Int. 2019;130:104360. DOI 10.1016/j.neuint.2018.12.011.
5. Appeltshauser L, Brunder A-M, Heinius A, et al. Antiparanodal antibodies and IgG subclasses in acute autoimmune neuropathy. Neurol Neuroimmunol Neuroinflamm. 2020;7:e817. DOI 10.1212/NXI.0000000000000817.

https://doi.org/10.1017/cjn.2021.256 Published online by Cambridge University Press