BMJ Neurology Open

‘Grasshopper sign’: the novel imaging of post-COVID-19 myelopathy with delayed longitudinal white matter abnormalities

Motohiro Okumura,[1] Kazumasa Sekiguchi ,[1] Tomoko Okamoto,[1] Reiko Saika,[1] Hiroyuki Maki,[2] Wakiro Sato,[3] Noriko Sato,[2] Takashi Yamamura,[3] Yuji Takahashi[1]

To cite: Okumura M, Sekiguchi K, Okamoto T, *et al*. ‘Grasshopper sign’: the novel imaging of post-COVID-19 myelopathy with delayed longitudinal white matter abnormalities. *BMJ Neurology Open* 2024;**6**:e000730. doi:10.1136/bmjno-2024-000730

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjno-2024-000730).

MO and KS contributed equally.

Accepted 03 June 2024

[1]Department of Neurology, National Center Hospital, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan
[2]Department of Radiology, National Center Hospital, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan
[3]Department of Immunology, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan

Correspondence to
Dr Yuji Takahashi; yutakahashi@ncnp.go.jp

ABSTRACT

Introduction Recently, there have been a few reports of atypical post-coronavirus disease 2019 (COVID-19) myelopathy manifesting tract-specific lesions similar to those due to vitamin B_{12} deficiency. However, the precise characteristics of imaging or clinical course remain not well understood.

Methods A retrospective analysis of the clinical and imaging characteristics of four patients who were referred to our hospital with a unique post-COVID-19 myelopathy was performed.

Results Four-to-six weeks following COVID-19 infection in the summer of 2023, four middle-aged men developed paraparesis, hypo/dysesthesia and bladder/bowel disturbance, suggesting myelopathy. Although spinal MRI showed no abnormalities in the early stages, tract-specific longitudinal lesions along the dorsal and lateral columns became apparent as the symptoms progressed. Owing to the lack of MRI findings at the early stage, all cases were challenging to diagnose. However, the patients remained partially responsive to aggressive immunosuppressive therapies, even in the advanced stage.

Discussion We termed these tract-specific longitudinal lesions in the presented case series ‘Grasshopper sign’ because brain coronal and spine axial MRI findings looked like a grasshopper’s antennae and face. Early identification of the characteristic MRI abnormality could allow for early intervention using intensive immunosuppressive therapy, which could improve patient outcomes.

INTRODUCTION

Neurological complications of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have been recognised. Specifically, myelopathy following the coronavirus infectious disease of 2019 (COVID-19) may worsen[1]; however, immunosuppressive therapy may be effective, leading to a favourable prognosis.[2] Following COVID-19, longitudinally extensive transverse myelopathy is often observed; however, the time course of the appearance of abnormal lesions on MRI, which may be negative at initial presentation, has not been evaluated.[1 3]

Here, we report a series of patients presenting myelopathy with delayed appearance of distinctive symmetrical longitudinal hyperintensity along the corticospinal tract and posterior column following COVID-19 infection.

METHODS

Between November 2023 and January 2024, four patients who developed myelopathy following COVID-19 infection were referred to our hospital. This report presents a retrospective analysis of the clinical and imaging characteristics of a unique myelopathy following COVID-19 infection.

RESULTS

Case 1

A 59-year-old man with a history of depression presented with a fever and was diagnosed with COVID-19 in June 2023. Five weeks later, the patient developed weakness in the lower limbs; however, brain and cervical MRI showed no abnormalities. His symptoms gradually worsened, leading to difficulty walking, weakness in the upper limbs and bladder/bowel disturbances. Four months following the COVID-19 diagnosis, T2-weighted imaging (T2WI)/fluid-attenuated inversion recovery (FLAIR) revealed abnormal signals along the corticospinal tract in the brain. Myelopathy was suspected and the patient was treated with steroid pulse therapy; however, his symptoms worsened, and he was referred to our hospital for further evaluation 6 months after COVID-19 infection.

Laboratory tests revealed no abnormalities as the cause of myelopathy. Cerebrospinal fluid (CSF) analysis revealed a mildly elevated protein level (67 mg/dL) but was negative for

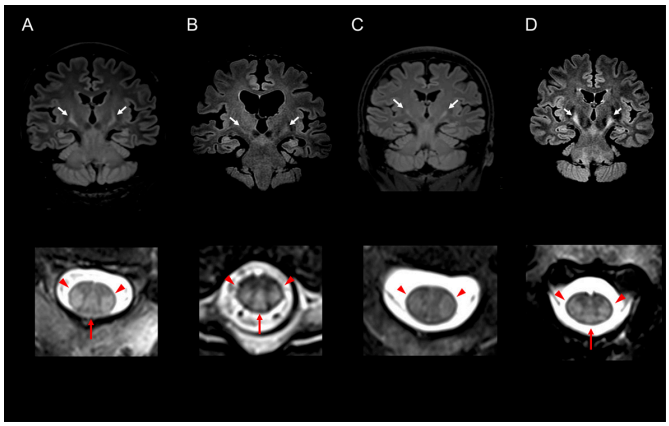

Figure 1 (A) MRI in case 1. Coronal brain FLAIR showed hyperintense signals along the corticospinal tracts from the posterior limb of the internal capsules, expanding bilaterally to the corona radiata (white arrow) without enhancement. Axial T2WI of C3 displayed hyperintensity involving the lateral and posterior columns bilaterally (red arrowhead and red arrow), which lasted throughout the spine. We termed this unique characteristic image 'Grasshopper sign' because these abnormalities looked like a grasshopper's face (spine) and antennae (brain). (B) MRI in case 2. Coronal brain FLAIR showed hyperintensity along the corticospinal tracts involving internal capsules (white arrow). Axial T2WI of T7 revealed hyperintensity involving lateral and posterior columns bilaterally (red arrowhead and red arrow). (C) MRI in case 3. Axial and coronal brain FLAIR showed hyperintensity along the corticospinal tracts (white arrow). Axial T2WI of C2 showed hyperintensity involving bilateral lateral columns and partially posterior columns (red arrowhead). (D) MRI in case 4. Coronal brain FLAIR and axial T2WI of C2 revealed a more apparent 'Grasshopper sign' compared with the other cases. C, cervical; FLAIR, fluid-attenuated inversion recovery; T, thoracic; T2WI, T2-weighted imaging.

oligoclonal band (OCB). Brain and spine MRI demonstrated characteristic symmetrical longitudinal hyperintensities in T2WI/FLAIR, affecting the corticospinal tract and posterior column from the brain throughout the spine (figure 1A). Additional intravenous immunoglobulin treatment and plasmapheresis were initiated. Finally, the patient showed gradual improvement in muscle strength of his limbs and could stand with some assistance.

Case 2

A previously healthy 59-year-old man who presented with fever and headache was diagnosed with COVID-19 in August 2023. The patient experienced urination difficulty 6 weeks after COVID-19 onset. He also developed paraparesis, hypoesthesia and dysesthesia in both lower legs; however, no obvious abnormal lesions were observed on the whole-spine MRI. No treatment was initiated and his symptoms worsened, resulting in an inability to stand. Subsequently, he was referred to our hospital for a follow-up examination 4 months after COVID-19 infection.

Neurological examination revealed spastic paraparesis with apparent pyramidal signs in both lower limbs, mild muscle weakness in both upper limbs, spinal automatic reflexes, hypoesthesia below the thoracic 10 level, disappearance of vibratory sensation in both lower extremities and bladder/bowel disturbances. His laboratory profile to rule out other myelopathies was negative. Furthermore, the CSF profile was normal. Brain and spine MRI showed bilateral hyperintensity along corticospinal tracts and posterior columns (figure 1B). He underwent steroid pulse therapy, plasmapheresis and intravenous immunoglobulin. At last, the patient showed dysesthesia disappearance and became able to stand with some assistance.

Case 3

A previously healthy 65-year-old man who presented with fever and fatigue was diagnosed with COVID-19 in September 2023. Six weeks after COVID-19 onset, bladder/bowel disturbances and lower limb dysesthesia gradually developed, followed by the inability to stand. An examination performed by neurologists revealed hypoesthesia and dysesthesia in the lower lumbar 2, decreased deep sensation, bladder/bowel disturbances and pyramidal signs. CSF analysis revealed mildly elevated basic myelin protein levels (MBP, 327 pg/mL). Repeated spinal MRI showed no abnormal lesions; however, brain MRI revealed faint hyperintensity in the bilateral posterior limbs of the internal capsules. Intravenous immunoglobulin and steroid pulse therapy were initiated; however, the progression of paraplegia made it difficult for the patient to stand. For further evaluation, the patient was transferred to our hospital 4 months after COVID-19 infection.

A spine MRI, performed in our hospital, revealed long hyperintensities in the lateral columns along the entire spinal cord, partly including the posterior columns (figure 1C). We administered plasmapheresis; the patient was eventually able to stand independently.

Case 4

A previously healthy 52-year-old man presented with fever, headache and muscle pain in August 2023. Although the patient did not undergo SARS-CoV-2 testing, his antibody level for SARS-CoV-2 was very high at the time of admission. Four weeks later, the patient experienced lower muscle weakness and bladder/bowel disturbances, followed by lower limb dysesthesia. Previous examinations by neurologists revealed paraplegia, pyramidal signs, hypoesthesia, dysesthesia in the lower limbs and bladder/bowel disturbances. CSF analysis revealed elevated protein (54 mg/dL) and MBP (500 pg/mL) levels. However, blood analysis and repeated MRI of the brain and spine revealed no abnormalities. Since the patient tested positive for OCB 3 weeks after hospitalisation, steroid pulse therapy and plasmapheresis were initiated. However, paraplegia worsened. Consequently, he was referred to our hospital for further examination 4 months after the COVID-19 infection.

Brain and cervical MRI in our hospital revealed a more apparent symmetrical longitudinal tract-specific hyperintensities in T2WI/FLAIR compared with cases 1–3 (figure 1D). Intravenous immunoglobulin was immediately administered. Finally, his dysesthesia disappeared, but paraplegia remained.

DISCUSSION

We reported a series of four cases exhibiting a severe form of myelopathy that developed following COVID-19 infection, with delayed appearance of distinctive bilateral longitudinal abnormalities along the corticospinal tract and posterior column. The tract-specific abnormalities such as those in our cases had been previously reported in individuals following COVID-19 infection or vaccination.[4–6] However, the distinctive points of our case series are as follows: (1) all cases involved middle-aged men following COVID-19 infection in the summer of 2023, (2) showing unique longitudinal MRI findings, which we termed the 'Grasshopper sign' because it resembled a grasshopper's face (spine) and antennae (brain), manifested with delayed clinical presentation and (3) immunosuppressive therapy could be partially effective, even in the long-term (online supplemental figure 1).

Since all these cases occurred in middle-aged Japanese men following COVID-19 infection in the summer of 2023, we speculate that the underlying mechanisms of myelopathy development are related to strain specificity and host susceptibility. Past reports suggested that there was a slight male predominance with a median age of 50 years in patients with myelopathy following COVID-19.[7 8] New SARS-CoV-2 XBB lineage mutants, with both F456L and L455F mutations, are expected to spread widely throughout Asia in the summer of 2023.[9] These mutations would enhance SARS-CoV-2 to the structural angiotensin-converting enzyme 2 (ACE2)-binding affinity and further immune activation.[9] The locus gene of ACE2, the target entry of SARS-CoV-2, is localised on the X chromosome, as well as genes related to inflammation and the release of inflammatory cytokines.[10] Consequently, men (who have a single X chromosome) may be more vulnerable to COVID-19 infection than women (who have two X chromosomes).[10] In addition, testosterone offers protective effects on the immune system; therefore, middle-aged men may present with severe myelopathy due to the intense immune response induced by the new SARS-CoV-2 strain.[11]

Signals similar to the 'Grasshopper sign,' are observed in white matter disorders such as adult-onset autosomal dominant demyelinating leukodystrophy,[12] mainly owing to disorders of oligodendrocytes.[13] This is consistent with the partial response to immunosuppressive therapy observed in our cases if oligodendrocyte dysfunction occurs initially, followed by secondary axonal degeneration. Thus, the drastic immune responses induced by COVID-19 infection could specifically trigger white matter damage; early medical intervention is crucial.

Subacute combined degeneration of the spinal cord due to vitamin B_{12} or copper deficiency also showed abnormal signals along the lateral and posterior columns of the spinal cord similar to the 'Grasshopper sign'.[14] However, our cases showed no significant abnormality in the serum level of vitamin B_{12} or copper. This could be explained by the fact that COVID-19 may affect the methylation cycle.[5 15]

In summary, the present case series described post-COVID-19 myelopathy with delayed appearance of longitudinal white matter abnormalities presenting with 'Grasshopper sign'. This characteristic sign is indicative of post-COVID-19 myelopathy and should prompt aggressive therapeutic interventions. The study findings could expand our current understanding of COVID-19-associated neuroimmunological disorders.

Acknowledgements The authors appreciate the following doctors for the examination and treatment in the previous hospitals: Dr Kenji Uchino (Department of Neurology, Kawasaki Municipal Tama Hospital), Dr Yusuke Oshita (Department of Orthopaedic Surgery, Showa University Northern Yokohama Hospital), Dr Yasushi Shiio, Dr Taro Bannai, Dr Yasufumi Hayashi (Department of Neurology, Tokyo Teishin Hospital), Dr Yoshio Sakiyama, Dr Michiko Tsutsumiuchi, Dr Kazuki Fujita, Dr Yu Matsuda, Dr Kenta Tominaga (Department of Neurology, Jichi Medical University Saitama Medical Center). The authors thank Mrs Hiromi Yamaguchi in the Department of Immunology, National Center Hospital, National Center of Neurology and Psychiatry, for the measurements of plasmablasts.The authors also appreciate Professor Winfried Stoecker and Dr Bianca Teegen for the measurement of antineural antibody.

Contributors Concept and design: MO, KS, TO, RS, YT. Drafting of the manuscript: MO, KS. Critical revision of the manuscript for important intellectual content; TO, RS, WS, NS, YT. Administrative, technical or material support: HM, WS, NS, TY. Supervision: HM, WS, NS, TY, YT.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. No data.

ORCID iD

Kazumasa Sekiguchi http://orcid.org/0009-0002-5105-5661

REFERENCES

1 Román GC, Gracia F, Torres A, *et al*. Acute transverse Myelitis (ATM):Clinical review of 43 patients with COVID-19-associated ATM and 3 post-vaccination ATM serious adverse events with

the Chadox1 nCoV-19 vaccine (Azd1222). *Front Immunol* 2021;12:653786.
2 Mondal R, Deb S, Shome G, *et al*. COVID-19 and emerging spinal cord complications: A systematic review. *Multiple Sclerosis and Related Disorders* 2021;51:102917.
3 Kawama K, Shimazaki R, Sunami Y, *et al*. Case report: MRI-negative Myelitis following COVID-19 with SEP abnormalities: a case series and literature review. *Front Neurol* 2023;14:1275696.
4 Memon AB, Al-Hader R, Patel S, *et al*. Late-onset rapidly progressive MRI- negative-Myelitis after COVID-19 illness. *Clinical Neurology and Neurosurgery* 2021;202:106513.
5 Huang HY, Shah LM, McNally JS, *et al*. COVID-19-associated Myelitis involving the dorsal and lateral white matter tracts: A case series and review of the literature. *AJNR Am J Neuroradiol* 2021;42:1912–7.
6 Mahajan A, Nayak MK, Gaikwad SB, *et al*. Post-vaccination/post-COVID immune-mediated Demyelination of the brain and spinal cord: A novel neuroimaging finding. *Neurol India* 2023;71:86–91.
7 Schulte EC, Hauer L, Kunz AB, *et al*. Systematic review of cases of acute Myelitis in individuals with COVID-19. *Eur J Neurol* 2021;28:3230–44.
8 Garg RK, Paliwal VK, Gupta A. Spinal cord involvement in COVID-19: A review. *J Spinal Cord Med* 2023;46:390–404.
9 Jian F, Feng L, Yang S, *et al*. Convergent evolution of SARS-Cov-2 XBB lineages on receptor-binding domain 455–456 synergistically enhances antibody evasion and Ace2 binding. *PLoS Pathog* 2023;19:e1011868.
10 Gemmati D, Bramanti B, Serino ML, *et al*. COVID-19 and individual genetic susceptibility/receptivity: role of Ace1/Ace2 genes, immunity, inflammation and coagulation. might the double X-Chromosome in females be protective against SARS-Cov-2 compared to the single X-Chromosome in males *Int J Mol Sci* 2020;21:3474.
11 Giagulli VA, Guastamacchia E, Magrone T, *et al*. Worse progression of COVID-19 in men: is testosterone a key factor *Andrology* 2021;9:53–64.
12 Sundblom J, Melberg A, Kalimo H, *et al*. MR imaging characteristics and neuropathology of the spinal cord in adult-onset Autosomal dominant Leukodystrophy with autonomic Aymptoms. *AJNR Am J Neuroradiol* 2009;30:328–35.
13 Rolyan H, Tyurina YY, Hernandez M, *et al*. Defects of lipid synthesis are linked to the age-dependent Demyelination caused by Lamin B1 overexpression. *J Neurosci* 2015;35:12002–17.
14 Briani C, Dalla Torre C, Citton V, *et al*. Cobalamin deficiency: clinical picture and radiological findings. *Nutrients* 2013;5:4521–39.
15 Wee AKH. COVID-19's toll on the elderly and those with diabetes mellitus – is vitamin B12 deficiency an accomplice. *Med Hypotheses* 2021;146:110374.