【 CASE REPORT 】

# Temporal Changes in Brain Perfusion in a Patient with Myoclonus and Ataxia Syndrome Associated with COVID-19

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**Abstract:**

Myoclonus and ataxia, with or without opsoclonus, have recently been recognized as a central nervous system syndrome associated with coronavirus disease-2019 (COVID-19). A 52-year-old Japanese man developed myoclonus and ataxia 16 days after the onset of COVID-19. Brain single-photon emission computed tomography (SPECT) revealed hyperperfusion in the cerebellum and hypoperfusion in the cerebral cortices with frontal predominance during the acute stage, which improved over two months. This study indicates that brain perfusion SPECT can be effective in detecting functional alterations in COVID-19-related myoclonus and ataxia.

**Key words:** myoclonus, ataxia, brain perfusion, COVID-19, Kampo

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## Introduction

Since the onset of the pandemic in 2020, neurological manifestations of coronavirus disease-2019 (COVID-19) have become more prevalent. Overall, the mechanisms underlying the neurological manifestations associated with COVID-19 are divided into three categories: (a) direct viral invasion of the nervous system, (b) parainfectious or postinfectious immune-mediated disease, and (c) manifestations secondary to the systemic effects of COVID-19, such as hypoxia with severe respiratory compromise or cerebrovascular events with vascular injury and thrombosis (1).

Acute-onset myoclonus and ataxia with or without opsoclonus are becoming increasingly evident as central nervous system involvements associated with COVID-19 (2, 3). The onset of neurological symptoms, a positive response to immunotherapy, and the absence of any abnormality on magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) examinations are suggestive of a postinfectious immune-mediated mechanism rather than direct viral en-

cephalitis (2, 3). Nevertheless, COVID-19-related myoclonus and ataxia can occur even during the acute phase of COVID-19 infection (2, 3), obscuring the substantiation of the pathogenesis (immune-mediated vs. direct viral invasion) based solely on the timing of the onset of neurological manifestations.

For further insight into the mechanisms underlying the neurological manifestations of COVID-19, the potential impact of nuclear medicine has been discussed (4). Although patients with COVID-19-related myoclonus and ataxia have been reported with brain metabolic abnormalities on 2-deoxy-2-fluoro-D-glucose (FDG) positron emission tomography-computed tomography (PET-CT) imaging (5, 6), no cases of myoclonus or ataxia syndrome with brain perfusion abnormalities on single-photon emission computed tomography (SPECT) have been reported.

We herein report a case of myoclonus and ataxia associated with COVID-19 and SPECT imaging findings of brain perfusion abnormalities.
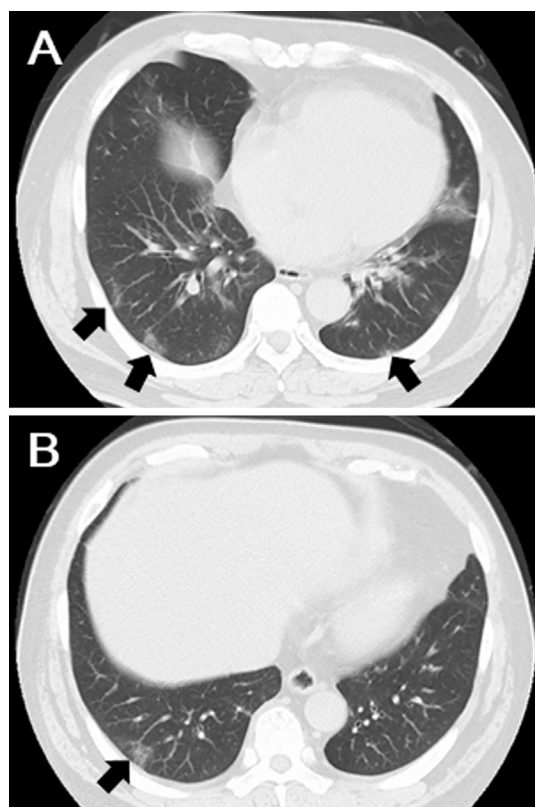
**Figure 1.   Chest computed tomography (CT) results. Chest CT (A, B) showed bilateral multifocal ground-glass opacities (black arrows).**

## Case Report

A 52-year-old Japanese man with a medical history of hypertension and hyperlipidemia was referred to the neurology department of our hospital because of jerky movements, posture and gait instability, and difficulty writing that had emerged after the resolution of COVID-19-related symptoms.

He developed a fever and cough on the first day. On day five, he was admitted to our hospital for worsening dyspnea and received low-flow nasal cannula oxygen therapy. Chest CT showed bilateral multifocal ground-glass opacities (Fig. 1). A reverse transcription-polymerase chain reaction (RT-PCR) test from a nasal swab confirmed COVID-19 lung infection. Thereafter, he completed a 5-day course of remdesivir, resulting in complete resolution of the aforementioned constitutional symptoms.

On day 16, he noticed mild jerky involuntary movements in all limbs along with difficulty in walking and writing. On day 18, he was discharged, but his neurological symptoms gradually worsened. On day 29, he was administered 7.5 g/day of Yokukan-san (YKS) extract, a Japanese traditional herbal medicine (Kampo). He was unable to walk without support and was admitted to our hospital for the second time on day 30.

A neurological examination revealed no signs of opso-clonus or consciousness disturbance. We examined the cranial nerves and found them to be unremarkable. We detected action-induced, posture-induced, and tactile stimuli-sensitive myoclonus in the trunk and all four limbs. There was no credible negative myoclonus. His gait was broad-based and unsteady, and he had cerebellar ataxia in all four limbs. The Scale for the Assessment and Rating of Ataxia (SARA) indicated a score of 12. Tendon reflexes were normal, and plantar reflexes were bilaterally flexor. We discovered no sensory abnormalities. The results of neuropsychological tests, including the Mini-Mental State Examination, Wechsler Adult Intelligence Scale-IV, Trail Making Test, and Behavioral Assessment of the Dysexecutive Syndrome, were mostly in the normal range (Table).

The blood test results, which included assessments of the thyroid function, were unremarkable. Additional tests for serum antinuclear antibodies, glutamic acid decarboxylase antibody, thyroid peroxidase antibodies, thyroglobulin, and anti-GQ1b ganglioside antibodies were all negative, but vitamin B1 and B12 levels were found to be decreased [vitamin B1, 17 ng/mL (reference range 24-60 ng/mL); vitamin B12, 139 pg/mL (reference range, 180-914 pg/mL)]. A CSF examination revealed a white blood cell count of 2 cells/mm$^3$ (all mononuclear cells), protein of 35 mg/dL, and glucose of 59 mg/dL (blood glucose=97 mg/dL). RT-PCR for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the CSF was negative.

Brain MRI without contrast revealed no abnormal signal lesions or atrophy. Electroencephalography showed no slow waves and epileptiform discharges. N-isopropyl-p-(123I)-iodoamphetamine (IMP) SPECT revealed hyperperfusion in the cerebellum and hypoperfusion in the cerebral cortices with frontal lobe predominance (Fig. 2). The patient was ultimately diagnosed with SARS-CoV-2 infection-related myoclonus and ataxia syndrome.

He was administered 2 series of intravenous high-dose methylprednisolone (IVMP, 1 g/day for 3 days), which started 19 days after the onset of neurological symptoms. His symptoms had significantly improved by the end of this treatment, with a SARA score of 6 (Fig. 3). Furthermore, we administered benfotiamine (103.74 mg/day), pyridoxine hydrochloride (75 mg/day), and cyanocobalamin (750 μg/day) as a combination. Follow-up IMP-SPECT obtained two months after the initial one showed improvement of cerebral blood flow abnormalities (Fig. 2). Follow-up neuropsychological tests obtained two months later revealed an improvement in the overall cognitive function (Table). The patient experienced complete resolution of myoclonus and ataxia with a SARA score of 0 at the last outpatient follow-up three months following the onset of neurological symptoms.

## Discussion

This is the first report of COVID-19-related myoclonus and ataxia in Japan and also the first to illustrate brain per-

**Table.**   **Results of Neuropsychological Evaluation.**

|  | On admission | Follow-up (after 2 months) |
|---|---|---|
| MMSE | 25 | 30 |
|  | (orientation -1, calculation -4) | |
| WAIS-IV | | |
|     Verbal comprehension | 104 (average) | 113 (bright normal) |
|     Perceptual reasoning | 99 (average) | 116 (bright normal) |
|     Working memory | 88 (dull normal) | 106 (average) |
|     Processing speed | 93 (average) | 114 (bright normal) |
|     Full-scale intelligence quotient | 96 (average) | 115 (bright normal) |
| Trail making test | | |
|     From A, s | 35 | 26 |
|     From B, s | 60 | 53 |
| BADS | | |
|     Rule shift cards test | 3 | 4 |
|     Action program test | 4 | 4 |
|     Key search test | 4 | 4 |
|     Temporal judgement test | 4 | 4 |
|     Zoo map test | 2 | 3 |
|     Modified six elements test | 1 | 3 |
|     Total profile score | 18 | 22 |

MMSE: Mini-mental State Examination, WAIS-IV: Wechsler Adult Intelligence Scale-IV, BADS: Behavioural Assessment of the Dysexecutive Syndrome
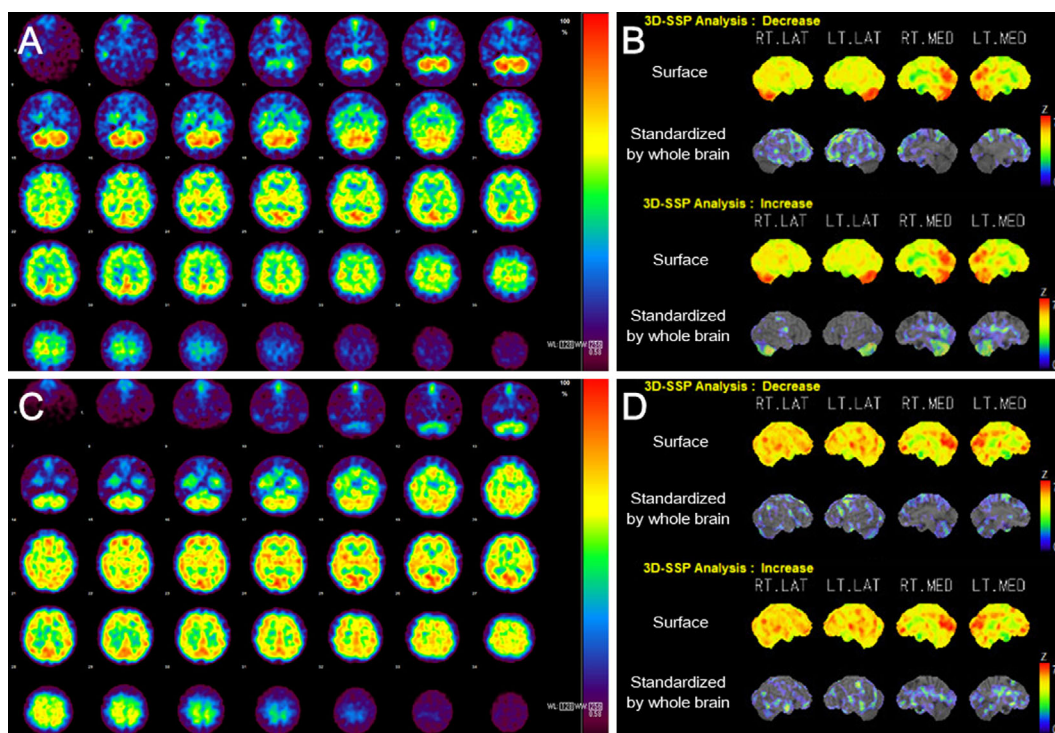


**Figure 2.**   **Brain N-isopropyl-p-($^{123}$I)-iodoamphetamine (IMP) single-photon emission computed tomography (SPECT) findings. IMP-SPECT obtained on admission (A) indicates hypoperfusion in the cerebral cortices with frontal predominance and hyperperfusion in the cerebellum. Furthermore, the areas of hypoperfusion and hyperperfusion on admission are shown on three-dimensional surface projection (3D-SSP) maps (B). Follow-up IMP-SPECT (C) and 3D-SSP maps (D) obtained two months after the initial one show an improvement in the abnormal perfusion pattern. LAT: lateral, LT: left, MED: median, RT: right**

fusion findings on SPECT in a patient with COVID-19-related myoclonus and ataxia. In this report, myoclonus and ataxia appeared after the resolution of infectious symptoms and improved after immunomodulatory treatment. Although
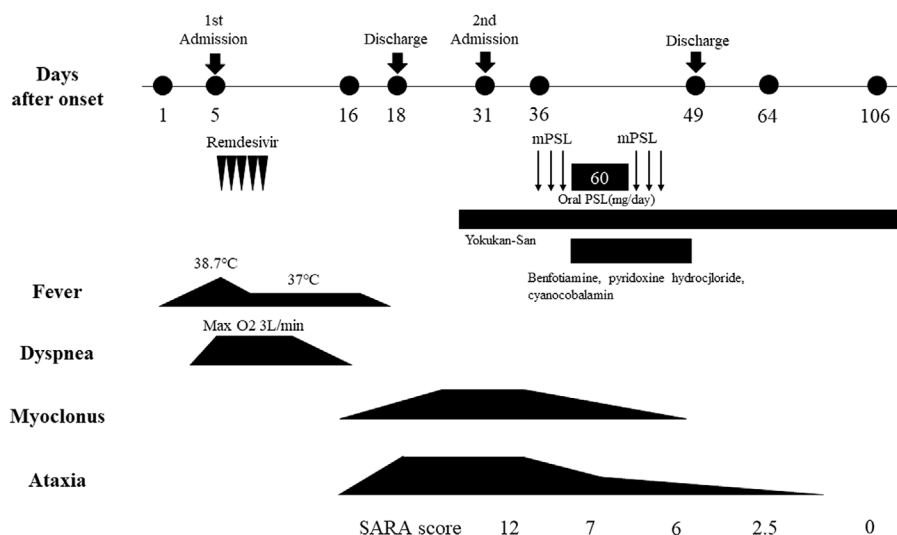
**Figure 3.** The clinical course of myoclonus and ataxia related to coronavirus disease. mPSL: methylprednisolone, PSL: prednisolone, SARA: Scale for the Assessment and Rating of Ataxia

the patient's neuropsychological test results on admission were mostly in the normal range, improved results on follow-up tests two months later revealed mild cognitive dysfunction in the acute phase.

COVID-19-related myoclonus and ataxia with or without opsoclonus may have been caused by parainfectious or postinfectious immune-mediated mechanisms. Although some patients present with myoclonus and ataxia during the acute phase of COVID-19 infection (2, 3), notably in our case, these symptoms appeared after the resolution of infectious symptoms of COVID-19. The subacute onset of myoclonus and ataxia after the disappearance of the typical infectious manifestations of COVID-19, a favorable response to IVMP treatment, the normality of MRI and CSF, and the negative result of RT-PCR testing for SARS-CoV-2 in CSF prompted us to postulate a postinfectious immune-mediated etiology rather than encephalitis caused by direct viral invasion.

As in our case, no previous case reports of myoclonus and ataxia with or without opsoclonus have shown CSF pleocytosis, and PCR tests for SARS-CoV-2 in the CSF were negative in all cases tested (2, 3, 5-19). Furthermore, brain MRI in previous case reports showed unremarkable results in almost all patients (2, 3, 5, 7-9, 11-19), except for one case that showed diffuse pachymeningeal enhancement (10). All previous cases were assumed to be associated with postinfectious or parainfectious complications of COVID-19 (2, 3, 5-19).

Although autoimmune and paraneoplastic antibodies were negative in cases of COVID-19-related myoclonus and ataxia with or without opsoclonus, a case of myoclonus and ataxia associated with COVID-19 had autoantibodies against Purkinje cells, striatal neurons, and hippocampal neurons in the serum and CSF (5). Opsoclonus-myoclonus-ataxia syndrome (OMAS) is characterized by a varied combination of opsoclonus, myoclonus, cerebellar ataxia, and behavioral and sleep disturbances (20). The myoclonus and ataxia described in the present study may have been on the OMAS spectrum. The pathophysiology of OMAS is considered to be immunologically based on paraneoplastic or parainfectious etiologies (20). Furthermore, metabolic abnormalities, hypoxia, and medication toxicity are thought to contribute to COVID-19-related myoclonus (2). However, in our case, there was no history of severe hypoxia or causative medication before the onset of neurological manifestations. Vitamin B1 and B12 deficiency are also unlikely to be the direct cause of myoclonus and ataxia, as the neurological symptoms tended to improve before supplementation.

Cerebellar hyperperfusion on SPECT observed in this case may have been related to an inflammatory or immune-mediated process. We observed an increased cerebellar blood flow on the initial SPECT findings, consistent with cerebellar dysfunction, and the improvement of perfusion abnormalities on follow-up SPECT also correlated with the patient's clinical recovery. Similar to our case, hypermetabolism in the cerebellum on FDG-PET/CT was reported in patients with COVID-19-related myoclonus and ataxia (5, 6). In addition, cerebellar hyperperfusion on SPECT and hypermetabolism on FDG-PET/CT have been reported in paraneoplastic cerebellar degeneration (21), OMAS (22, 23), and cerebellitis (24, 25).

Hypoperfusion in the cerebral cortices with frontal lobe predominance on SPECT may reflect functional impairment due to disruption of the cerebro-cerebellar network, which may explain the mild cognitive impairment observed in this case. Recent anatomical, clinical, and imaging findings have indicated that disruption in the cerebellar component of the cerebro-cerebellar circuits causes impairment in thought coordination, also termed cerebellar cognitive affective syndrome, which is similar to motor coordination impairment (26). Functional connectivity studies indicate that the cerebellum contributes to functional networks that include not just sensorimotor areas engaged in motor control but also association cortices involved in cognitive proc-

esses (27, 28). Task-based functional MRI studies have shown that cognitive tasks activate the posterior cerebellum as well as the prefrontal and parietal cortices (29, 30).

There are inconsistencies regarding the therapeutic strategies used for COVID-19-related myoclonus and ataxia across the literature, which have mostly consisted of symptomatic treatment with anti-epileptic medications and immunotherapies directed at a postinfectious immune-mediated mechanism (2). In addition, most reported cases of myoclonus and ataxia associated with COVID-19 received high-dose systemic steroids (mainly IVMP) and/or intravenous immunoglobulin and responded well (2). Since our patient was not ambulatory due to his myoclonus and ataxia on admission, we administrated IVMP treatment, which resulted in a significant improvement, as reported in previous studies. Nevertheless, we cannot deny that the myoclonus and ataxia in our patient may have improved along with the natural course of the disease.

Although the patient's neurological symptoms improved significantly at the start of steroid treatment, the clinical nadir of neurological symptoms was reached and followed by a plateau phase before the start of steroid treatment in this report. COVID-19-related myoclonus and ataxia cases that improved only by symptomatic treatment with anti-epileptic medications have been reported (8, 10). Therefore, depending on the severity of the clinical manifestations, symptomatic treatment alone may be considered in ambulatory patients (8). We also administered YKS before IVMP to our patient after the onset of his neurological symptoms. YKS consists of seven herbs (Japanese *Angelica* root, *Atractylodes lancea* rhizome, *Bupleurum* root, *Poria sclerotium*, *Glycyrrhiza* root, *Cnidium* rhizome, and *Uncaria* hook). This formula is considered to have some effects on the excitability of nerves, stabilize mental activities, and ameliorate involuntary muscle movements (31). Unfortunately, a quantitative or semi-quantitative evaluation of myoclonus and ataxia before and after YKS administration was not performed; therefore, the therapeutic effects of YKS, in this case, remain uncertain.

The present case indicates that brain perfusion IMP-SPECT may be effective in detecting functional alteration in COVID-19-related myoclonus and ataxia.

**The authors state that they have no Conflict of Interest (COI).**

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