Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.9308-22
Intern Med 61: 1761-1765, 2022
http://internmed.jp

【 CASE REPORT 】

The Immediate Onset of Isolated and Unilateral Abducens Nerve Palsy Associated with COVID-19 Infection: A Case Report and Literature Review

Takafumi Kubota[1], Naoto Sugeno[1], Hirohito Sano[2], Koji Murakami[2], Kensuke Ikeda[1], Tatsuro Misu[1] and Masashi Aoki[1]

Abstract:
Cranial nerve palsy associated with coronavirus disease 2019 (COVID-19) is rare. We herein report the first Asian case of the immediate onset of isolated and unilateral abducens nerve palsy (ANP) accompanied with COVID-19 infection. A 25-year-old man developed diplopia one day after the COVID-19 symptom onset. Neurological examination revealed limitation of left eye abduction without ataxia and hyporeflexia. Negative anti-ganglioside antibody results and mild albuminocytological dissociation were noted. The patient was diagnosed with left ANP accompanied by COVID-19 infection. The ANP spontaneously recovered without treatment. ANP can develop during the early phase of COVID-19 infection and adversely affect patients' quality of life.

Key words: COVID-19, SARS-CoV-2, neurological complication, abducens nerve palsy, Miller Fisher syndrome, anti-GQ1-b antibody

(Intern Med 61: 1761-1765, 2022)
(DOI: 10.2169/internalmedicine.9308-22)

Introduction

Abducens nerve palsy (ANP) is a neurological condition that manifests as horizontal diplopia. The etiology of ANP can include trauma, vascular disease, tumor, aneurysm, infection, and inflammatory diseases. Recent data from the insurance database of a neighboring country suggested that the incidence of ANP increases with age, and the etiology of ANP was presumed to be mainly vascular (56.6%), idiopathic (27.2%), neoplastic (5.6%), or traumatic (4.9%) (1). In addition, ANP can be induced by inflammatory and autoimmune mechanisms, and some cases of post-infectious ANP accompanied by cerebellar ataxia and hyporeflexia, which are known as Miller-Fisher syndrome (MFS), have been reported (2).

Coronavirus disease 2019 (COVID-19) infection causes isolated ANP in rare cases (3-6). We herein report the first Asian case of immediate-onset isolated and unilateral ANP accompanying COVID-19 infection.

Case Report

A 25-year-old Asian (Japanese) man working in the security department developed a fever. He had no history of diseases other than atopic dermatitis. The morning after the onset of the fever, he experienced double vision when he looked to the left. As diagnostic quantitative polymerase chain reaction for severe acute respiratory syndrome coronavirus 2 was positive, he isolated at a recovery accommodation facility.

He developed a cough on day five and was admitted to our COVID-19 ward on day six because he experienced difficulties in daily life due to diplopia and decreased appetite. A neurological examination revealed limitation of abduction in the left eye without ataxia and hyporeflexia (Fig. 1A). Hematological and biochemical analyses showed normal findings, including Hemoglobin A1c 5.5% (normal range:

[1]Department of Neurology, Tohoku University Graduate School of Medicine, Japan and [2]Department of Respiratory Medicine, Tohoku University Graduate School of Medicine, Japan
Received for publication January 6, 2022; Accepted for publication February 13, 2022
Correspondence to Dr. Naoto Sugeno, sugeno@med.tohoku.ac.jp

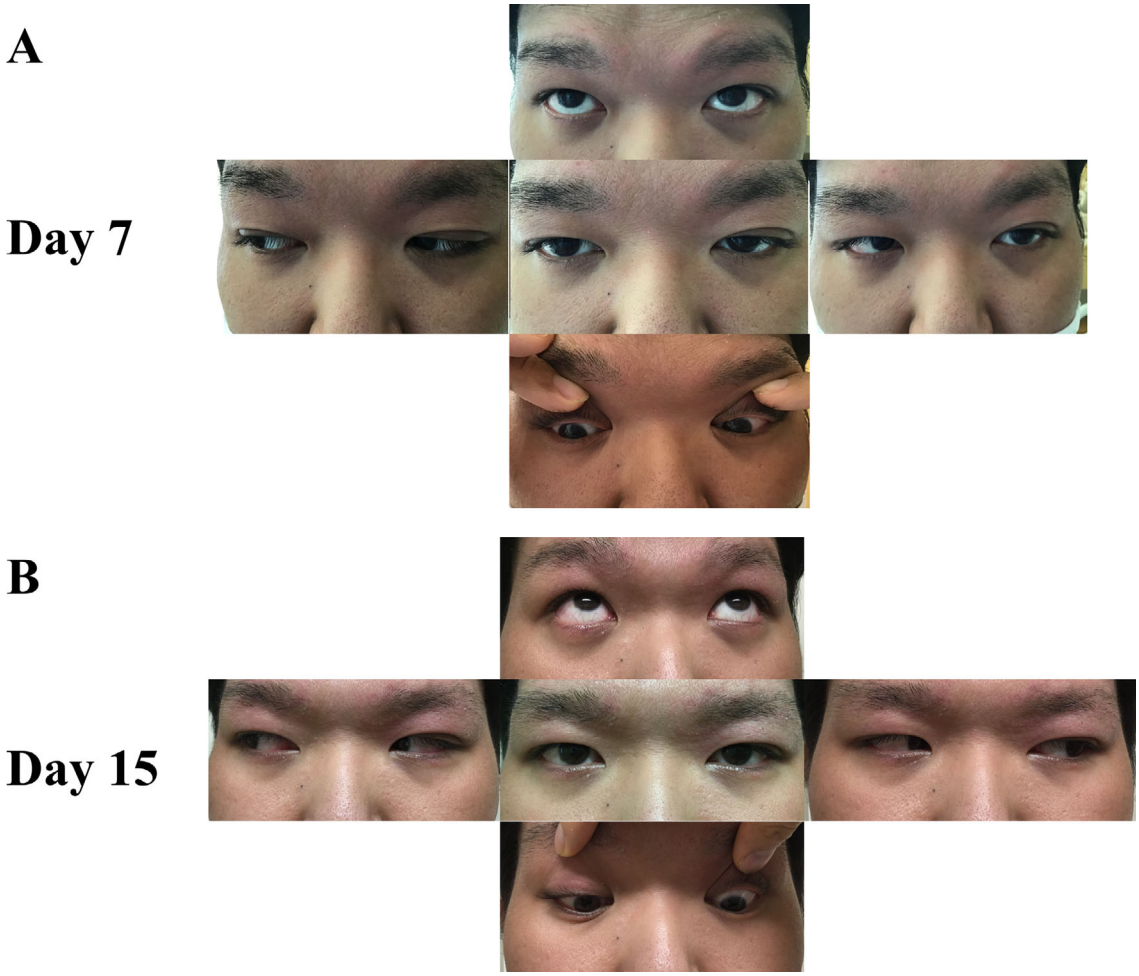

Figure 1. **Eye movement of the patient demonstrating left abducens nerve palsy. (A) The limitation of abduction in the left eye on day seven. (B) The limitation of abduction improved on day 15.**

<6.5%), free T3 2.89 pg/dL (normal range: 2.3-4.0 pg/dL), free T4 1.12 ng/dL (normal range: 0.9-1.7 ng/dL), human thyroid-stimulating hormone (hTSH) 2.18 μIU/mL (normal range: 0.5-5.0 μIU/mL), prothrombin time 107.5% (normal range: 80.0-120.0%), activated partial thromboplastin time 29.7 seconds (normal range: 24.3-36.0 seconds), and D-dimer <0.5 μg/mL (normal range: <1.0 μg/mL). There were some abnormal values, such as a mild elevation of C-reactive protein at 2.15 mg/dL (normal range: ≤0.3 mg/dL), immunoglobulin (Ig)A at 475 mg/dL (normal range: 110-410 mg/dL), total IgE at 9,941 IU/mL (≤170 IU/mL), CH50 at 68.5 CH/mL (normal range: 30-46 CH50/mL), and soluble interleukin-2 receptor (IL-2R) at 1,103 U/mL (normal range: 121-613 U/mL). Anti-GQ1b IgG antibody, anti-ganglioside GM1 antibody, antinuclear antibodies, perinuclear antineutrophil cytoplasmic antibody (ANCA), cytoplasmic ANCA, and acetylcholine receptor antibodies were negative. Anti-aquaporin 4 (AQP4) antibody and anti-myelin oligodendrocyte glycoprotein (MOG) antibody results were negative using the in-house cell-based assay (7). Cerebrospinal fluid showed null cell counts, IgG index 0.56 (normal range: <0.73), and protein levels of 55 mg/dL (normal range: 10-40 mg/dL).

Gadolinium-enhanced magnetic resonance imaging did not detect any abnormality in the cranial nerves or nuclei, cavernous sinus, or orbital apex, suggesting that the tests were negative for aneurysm, tumor, and inflammation (Fig. 2). Nerve conduction study in the limbs showed normal results. The patient was diagnosed with isolated, unilateral ANP associated with COVID-19 infection.

The limitation of the abduction in the left eye improved gradually. Because the symptoms recovered spontaneously, we did not provide any specific treatment, such as intravenous immune globulin (IVIG). Figure 1B shows the improvement on day 15. The patient was discharged on day 20 and followed at an outpatient clinic. He returned to his office and started working again on day 78.

Discussion

COVID-19 can cause a variety of cranial nerve palsies. In a systematic review of isolated cranial nerve involvement in COVID-19 patients, the number of cases was I (2), II (7), III (2), IV (0), V (2), VI (6), VII (16), VIII (1), IX (2), X (2), XI (0), and XII (2), respectively [cranial nerve (number of patients)] (8). As shown, the facial nerve is likely more vulnerable to COVID-19 infection than others, and the second-most susceptible cranial nerve was the abducens

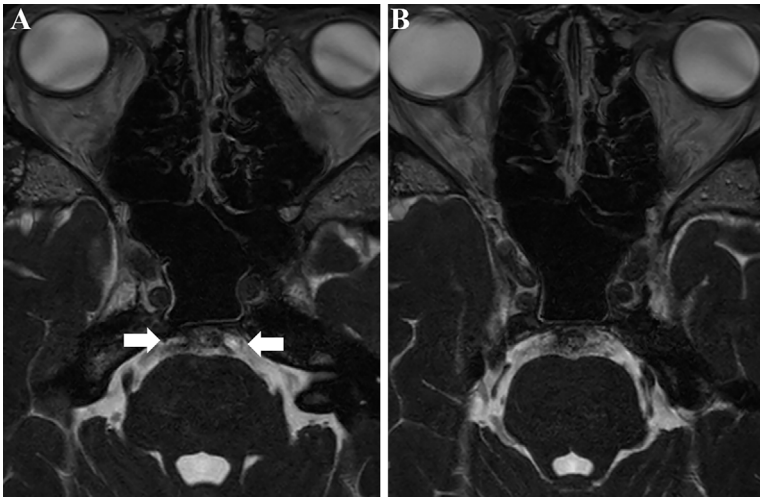

Figure 2. Gadolinium-enhanced constructive interference in steady-state magnetic resonance imaging. (A) No abnormalities in the abducens nerves (white arrow) or nuclei were noted. (B) No abnormalities in the cavernous sinus and orbital apex were noted.

nerve. Although the reasons for this selectivity are unclear, the pathomechanism involved, such as direct nerve invasion, local inflammation, ischemia, systemic inflammation, and autoimmunity, may influence the differences in features.

ANP is a cranial nerve palsy and manifests as disturbed external rotation of the corresponding eye. Various conditions, such as stroke or minor injury, can induce ANP (1). Among them, the most common cause of ANP after infection is well described as a component of the triad for MFS, consisting of ophthalmoplegia, cerebellar ataxia, and hyporeflexia. MFS is an immune-mediated disease, with positive results for anti-GQ1b IgG antibodies found in approximately 90% of MFS cases (2). ANP as a symptom of MFS shows that anti-GQ1b IgG antibodies cause neuronal damage (2).

COVID-19-induced ANP shares a post-infectious temporal course with MFS. Although the anti-GQ1b IgG antibody result was positive in approximately 90% of MFS cases reviewed (2), previous cases with COVID-19-induced ANP with this antibody have never been reported (3, 9-12). Only 11 cases with COVID-19 associated ANP have been reported to date (Table) (3-6, 9-13), indicating that there is insufficient evidence to conclude that COVID-19-associated ANP is not mediated by anti-GQ1b IgG antibody. The following observations may help distinguish between these two kinds of ANPs: neurological symptoms of MFS usually appear around 8 days (range: 1-30) after infection (2), whereas ANP associated with COVID-19 infection develops at a median of 4 days (range: 3-27) after infection (3-6, 9-13). The duration of symptoms following the infection was short in the current case, lasting for just one day, which is usually not enough for the antibody production to trigger post-infectious autoimmune diseases.

Although the availability of such cases in the literature is limited, we can discuss the possibility that ANP associated with COVID-19 infection may be associated with para-infectious inflammatory mechanisms different from anti-GQ1b IgG antibody, as there are several case reports of para-infectious ANP related to viral infections, including herpes zoster and dengue fever (14, 15). Our case also had albuminocytological dissociation in the cerebrospinal fluid as the sign of inflammation in the central nervous system. Therefore, some para-infectious inflammation could not be ruled out completely because of the possibility that COVID-19 activates unusual immune responses targeting unknown antigens.

Additionally, we asked the possibility of stroke-associated ANP caused by COVID-19 infection. Indeed, vascular problems were frequently observed in an ANP cohort study (1). In a recent study focusing on hospitalized COVID-19 patients with neurological disorders, cerebrovascular events were particularly prominent in cases of severe lung damage, which was accompanied by increased C-reactive protein and D-dimer levels. Although the involvement of eye movement disorder was observed in only 1.33% of individuals in this cohort, most of these cases were seen in the non-severe group (16). These findings suggest that cerebrovascular events do not always correlate with eye movement disorders.

As in the current case, even if major symptoms of COVID-19 infection, such as a fever, cough, and malaise, are not severe, diplopia due to ANP can cause significant difficulties in daily life. Every clinician should be aware of ANP associated with COVID-19 infection as a possible comorbidity and carefully monitor the course of the infection. For these patients, early consultation with a neurologist is highly recommended, as IVIG treatment may be necessary for patients that do not recover spontaneously.

Conclusion

Isolated and unilateral ANP can develop during the early phase of COVID-19 infection and may adversely affect the patient's quality of life. Clinicians should be aware of ANP associated with COVID-19 infection and carefully monitor

Table. **Abducens Nerve Palsy Associated with COVID-19 Infection.**

	Previous COVID-19 cases	Present case
Reference number	3-6, 9-13	NA
n	11	1
Age, median (range)	44 (32-71)	26
Male, n (%)	3 (23.1)	1
Area	Europe 8 (63.6), North America 4 (36.4)	Japan
Duration from COVID-19 symptoms to diplopia, median (range)	4 days (3-27)	1 day
ANP, n (%)	Bilateral VI 5 (45.5), unilateral VI 4 (36.4), III+VI 2 (18.2)	Unilateral VI
Other neurological signs, n (%)	None (only ophthalmoplegia) 5 (45.2), paresthesia 4 (36.4), Hyporeflexia 4 (36.4), ataxia/dysmetria 2 (18.2), weakness 3 (27.3), others 2 (18.2)	None (only ophthalmoplegia)
CSF, n (%)	Normal 6 (54.5) Albuminocytologic dissociation 2 (18.2), NA 3 (27.3)	Albuminocytologic dissociation
Anti-ganglioside antibodies, n (%)	Negative 5 (45.5), NA 5 (45.5), anti-GM 1 antibody 1 (9.1)	Negative
NCS, n (%)	NA 10 (90.9), demyelination 1 (9.1)	Normal
MRI, n (%)	Enhancement/hyperintensity in other parts 5 (45.5), normal 4 (36.4), enhancement/hyperintensity in VI 2 (18.2), NA 1 (7.7)	Normal
Treatment, n (%)	None 7 (63.6), IVIG 4 (36.4)	None
Outcome, n (%)	Some improvement 5 (45.5), complete improvement 3 (27.3), no change 2 (18.2)	Almost complete improvement

n: number of patients, COVID-19: coronavirus disease 2019, NA: not available, ANP: abducens nerve palsy, CSF: cerebrospinal fluid, NCS: nerve conductive study, MRI: magnetic resonance imaging, IVIG: intravenous immunoglobulin

the course of COVID-19 infection. Further cases and analyses will be required to elucidate the mechanism involved in COVID-19-induced ANP.

A written consent from the patient was obtained.

Data will be made available on reasonable request.

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

Acknowledgement

We thank all of the staff of the COVID-19 wards and the neurology medical wards of Tohoku University Hospital.

References

1. Jung EH, Kim SJ, Lee JY, Cho BJ. The incidence and etiology of sixth cranial nerve palsy in Koreans: a 10-year nationwide cohort study. Sci Rep **9**: 1-7, 2019.
2. Mori M, Kuwabara S, Fukutake T, Yuki N, Hattori T. Clinical features and prognosis of Miller Fisher syndrome. Neurology **56**: 1104-1106, 2001.
3. Dinkin M, Gao V, Kahan J, et al. COVID-19 presenting with ophthalmoparesis from cranial nerve palsy. Neurology **95**: 221-223, 2020.
4. Falcone MM, Rong AJ, Salazar H, Redick DW, Falcone S, Cavuoto KM. Acute abducens nerve palsy in a patient with the novel coronavirus disease (COVID-19). J AAPOS **24**: 216-217, 2020.
5. Gutiérrez-Ortiz C, Méndez-Guerrero A, Rodrigo-Rey S, et al. Miller Fisher syndrome and polyneuritis cranialis in COVID-19. Neurology **95**: e601-e605, 2020.
6. Anilkumar A, Tan E, Cleaver J, Morrison HD. Isolated abducens nerve palsy in a patient with asymptomatic SARS-CoV-2 infection. J Clin Neurosci **89**: 65-67, 2021.
7. Sato DK, Callegaro D, Lana-Peixoto MA, et al. Distinction between MOG antibodypositive and AQP4 antibody-positive NMO spectrum disorders. Neurology **82**: 474-481, 2014.
8. Finsterer J, Scorza FA, Scorza C, Fiorini A. COVID-19 associated cranial nerve neuropathy: a systematic review. Bosn J Basic Med Sci **22**: 39-45, 2021.
9. Pascual-Goñi E, Fortea J, Martínez-Domeño A, et al. COVID-19-associated ophthalmoparesis and hypothalamic involvement. Neurol Neuroimmunol Neuroinflamm **7**: e823, 2020.
10. Lantos JE, Strauss SB, Lin E. COVID-19-associated Miller Fisher syndrome: MRI findings. Am J Neuroradiol **41**: 1184-1186, 2020.
11. Manganotti P, Pesavento V, Buoite Stella A, et al. Miller Fisher syndrome diagnosis and treatment in a patient with SARS-CoV-2. J Neurovirol **26**: 605-606, 2020.
12. Reyes-Bueno JA, García-Trujillo L, Urbaneja P, et al. Miller-Fisher syndrome after SARS-CoV-2 infection. Eur J Neurol **27**: 1759-1761, 2020.
13. Ray A. Miller Fisher syndrome and COVID-19: is there a link. BMJ Case Rep **13**: 19-22, 2020.
14. Herath HMM, Hewavithana JS, De Silva CM, Kularathna OAR, Weerasinghe NP. Cerebral vasculitis and lateral rectus palsy-two rare central nervous system complications of dengue fever: two case reports and review of the literature. J Med Case Rep **12**: 1-6,

2018.

15. Cunniffe HA, Cunniffe NG. Herpes zoster oticus with meningitis masquerading as malignant otitis externa. BMJ Case Rep **12**: 10-12, 2019.

16. Gogu AE, Motoc AG, Stroe AZ, et al. Clinical spectrum and neuroimagistic features in hospitalized patients with neurological disorders and concomitant coronavirus-19 infection. Brain Sci **11**: 1138, 2021.