

**[ CASE REPORT ]**

# Autoimmune Glial Fibrillary Acidic Protein Astrocytopathy Presenting with Slowly Progressive Myelitis and Longitudinally Extensive Spinal Cord Lesions

Takuya Kudo, Akio Kimura, Kazuhiro Higashida, Megumi Yamada,  
Yuichi Hayashi and Takayoshi Shimohata

**Abstract:**

We report a 65-year-old man with autoimmune glial fibrillary acidic protein astrocytopathy (GFAP-A) who presented with gait disturbance that he had experienced for approximately half a year. On neurological examination, he displayed spastic paraplegia and autonomic dysfunctions including dysuria and constipation. Spinal cord magnetic resonance imaging showed longitudinally extensive spinal cord lesions (LESCLs) extending from the cervical to the thoracic cords. The patient was negative for anti-myelin oligodendrocyte glycoprotein and anti-aquaporin 4 antibodies. Treatment with corticosteroids and intravenous immunoglobulin resulted in a clinical improvement. It is important to distinguish GFAP-A from slowly progressive myelitis with LESCLs.

**Key words:** astrocytopathy, autoantibody, glial fibrillary acidic protein (GFAP), longitudinally extensive spinal cord lesion (LESCL), myelitis, neuromyelitis optica spectrum disorders (NMOSDs)

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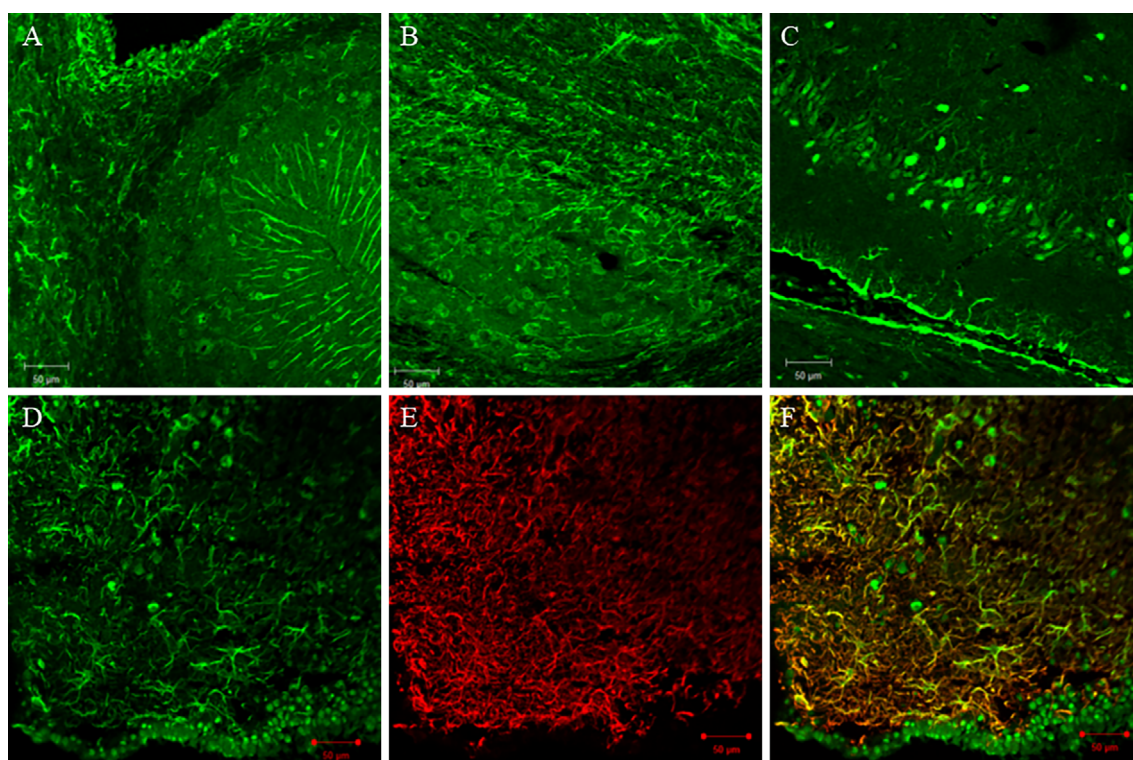
## Introduction

Autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy (GFAP-A) was recently reported as a spectrum of autoimmune inflammatory central nervous system disorders that is positive for GFAP-IgG in the cerebrospinal fluid (CSF) (1). Linear perivascular radial gadolinium-enhancement patterns on brain magnetic resonance imaging (MRI) are a hallmark of these disorders and they are sometimes observed in GFAP-A patients (2). The most common clinical syndrome of GFAP-A is meningoencephalitis (3, 4). Patients with GFAP-A usually present with headache and fever followed by consciousness disturbance and meningeal signs (2). Movement disorders including tremor and myoclonus, ataxia, hyperreflexia, autonomic dysfunction, and blurred vision related to optic disc edema are sometimes observed (2, 3). However, 5% of GFAP-A patients present with isolated myelitis (4). We herein report a GFAP-A patient with slowly progressive myelitis with longitudinally ex-

tensive spinal cord lesions (LESCLs).

## Case Report

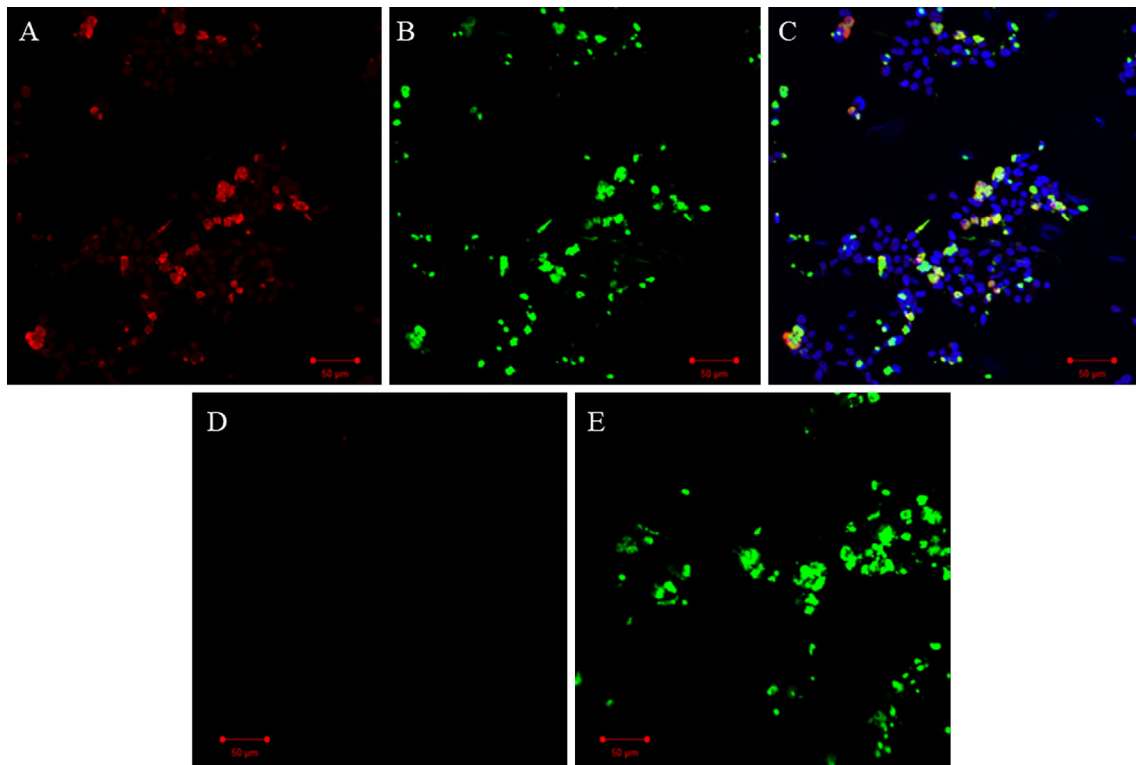
A 65-year-old man visited a local hospital suffering from fever, headache, loss of appetite, weight loss, and disorientation for approximately the previous 22 months before admission to our hospital. These symptoms lasted for approximately 3 months and then they spontaneously improved. About six months before admission to our hospital, he stumbled on a block in a station and fell. While walking, he had difficulty in raising both knees and moving his legs forward smoothly. His gait disturbance slowly progressed, and he then visited a local hospital about 3 months before admission to our hospital. Hereditary spastic paraplegia was suspected, and he was referred to our hospital. He had no remarkable past or family history. On neurological examination, his level of consciousness was normal. His cognitive functions were normal, and his Mini-Mental State Examination score was 29 points. He showed no cranial nerve abnor-



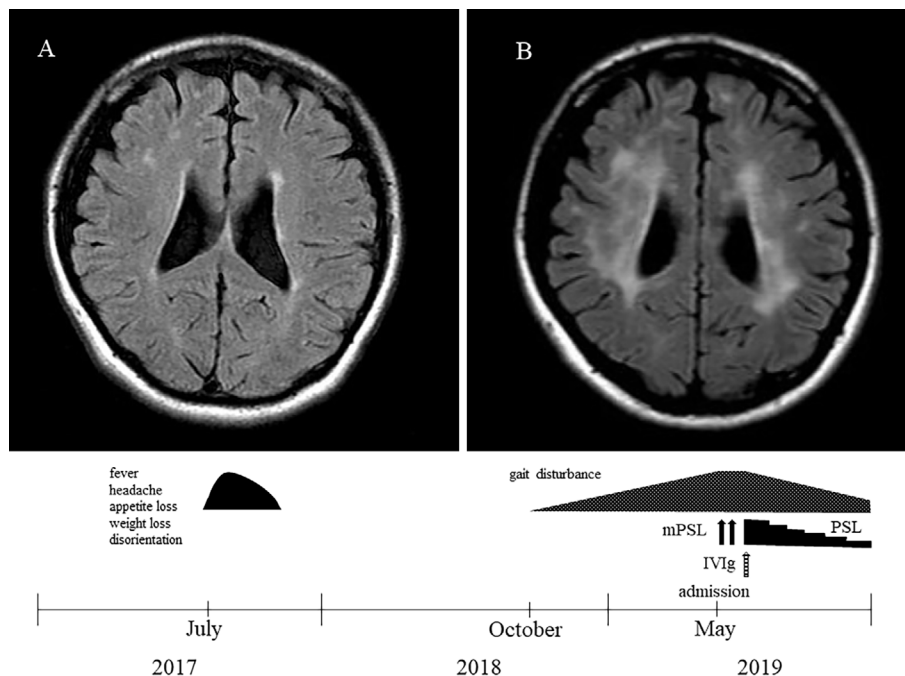
**Figure 1.** Detection of CSF GFAP-IgG by tissue-based immunofluorescence assays. Immunoreactivity of cerebrospinal fluid (CSF)-IgG from our patient with autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy was observed in astrocytes of rat cerebellum (A), brainstem (B), hippocampus (C), and periventricular regions (D). Astrocytes stained with a commercial anti-GFAP antibody (ab207165, Abcam, Cambridge, UK) (E). Colocalization of the patient's CSF-IgG and the commercial anti-GFAP antibody is shown in yellow in the merged images (F).

malities. Manual muscle tests were normal except for proximal lower limbs (gluteus 4/4, iliopsoas 3/3). His bilateral patella and Achilles tendon reflexes were hyperactive, and bilateral Chaddock reflexes were positive. The muscle tonus of his lower limbs was spastic. Coordination of the upper limbs and sensations including soft touch, pain, and vibrations of the whole body were normal. He presented with autonomic dysfunctions including dysuria and constipation. He presented with spastic gait and needed a walking frame. He had no meningeal signs. He complained of no visual acuity or field impairment. A fundus examination by an ophthalmologist was normal. Laboratory tests showed a normal number of white blood cells and no elevation of C-reactive protein levels. The serum levels of folic acid, vitamin B1, vitamin B12, soluble interleukin 2 receptor, lysozyme, angiotensin converting enzyme, and very long chain fatty acids were normal. We investigated the presence of autoantibodies, including anti-nuclear antibodies, anti-double stranded DNA IgG antibodies, anti-Smith antibodies, anti-SS-A antibodies, anti-SS-B antibodies, serine proteinase 3-anti-neutrophil cytoplasmic antibodies (PR3-ANCA), myeloperoxidase-anti-neutrophil cytoplasmic antibodies (MPO-ANCA), anti-cyclic citrullinated peptide antibodies, anti-myelin oligodendrocyte glycoprotein (MOG) antibodies, and anti-aquaporin 4 (AQP4) antibodies. All were absent from his serum. He was also negative for anti-human T-cell

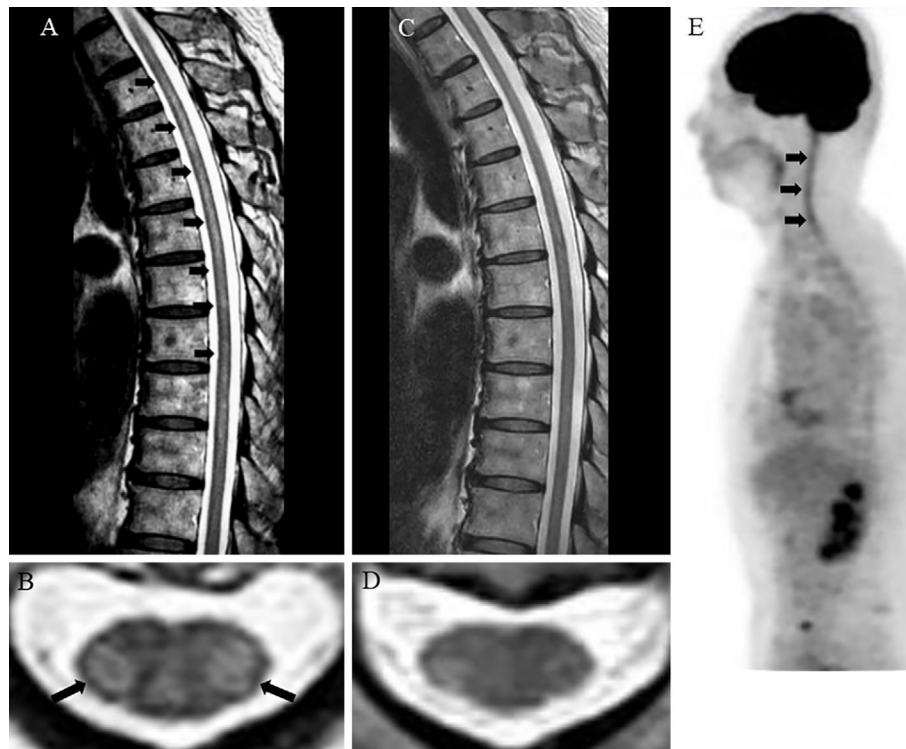
leukemia virus type 1 (HTLV-1) antibodies. A CSF analysis showed an increased number of cells [13 cells/mm<sup>3</sup> (mononuclear cells); normal <5 cells/mm<sup>3</sup>], elevated protein levels (54 mg/dL; normal <50 mg/dL), and interleukin (IL) 6 levels (10.1 pg/mL). The CSF IgG index was elevated (0.78; normal <0.75), and the oligoclonal bands were positive. We investigated CSF GFAP-IgG using immunohistochemistry and a cell-based assay as previously reported (3). Strong immunoreactivity was observed with the CSF sample against astrocytes in the cerebellum, brainstem, hippocampus, and periventricular regions of rat brain (Fig. 1). We confirmed the presence of CSF GFAP-IgG using a cell-based assay with HEK293 cells expressing GFAP $\alpha$  (Fig. 2). Brain MRI on admission and again about 3 months before admission to our hospital showed extended white matter hyperintensity lesions in the subcortical and deep white matter on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images (Fig. 3B). However, brain MRI at 22 months before admission showed only mild T2 and FLAIR hyperintensity lesions in the subcortical white matter (Fig. 3A). Spinal cord MRI showed longitudinally extensive T2-hyperintensity lesions with an obscure margin extending from the cervical to the thoracic cords (Fig. 4A). The spinal cord MRI T2 axial images showed hyperintensities in the lateral columns bilaterally (Fig. 4B). Contrast enhanced brain and spinal cord MRI showed no abnormal enhancement. Positron emission



**Figure 2.** Detection of CSF GFAP-IgG by transfected cell-based assays. HEK293 cells stably expressing green fluorescent protein (GFP)-tagged GFAP $\alpha$  (B, E). Glial fibrillary acidic protein (GFAP)-IgG was detected in the cerebrospinal fluid (CSF) of this patient (1: 4, A), but not in the CSF of a control patient (psychosomatic disorder; 1: 4, D). Colocalization of the patient's IgG and GFAP $\alpha$  is shown in yellow in the merged images (C). DNA is stained with Hoechst 33342 (blue).



**Figure 3.** Brain MRI and the clinical course. Fluid-attenuated inversion recovery (FLAIR) MRI of the brain at 22 months before admission showed only mild hyperintensity lesions in the subcortical white matter (A). Nineteen months later, it showed extended white matter hyperintensity lesions in the subcortical and deep white matter (B).



**Figure 4.** Spinal cord MRI and positron emission tomography/computed tomography with 18F-fluorodeoxyglucose (18F-FDG PET/CT). Spinal cord MRI before immunotherapy showed longitudinally extensive T2-hyperintensity lesions with an obscure margin extending from the cervical to the thoracic cords (arrows) (A). The T2 axial sequence of the spinal cord MRI showed hyperintense signal changes involving the lateral columns of the cervical cord bilaterally (arrows) (B). MRI T2-hyperintensity lesions of the spinal cord showed improvements about 4 months after starting the corticosteroid treatment (C, D). 18F-FDG PET/CT showed the accumulation of FDG in the cervical and thoracic cords (arrows) (E).

tomography / computed tomography with 18 F-fluorodeoxyglucose (18F-FDG PET/CT) was performed to try and identify any malignancy. FDG accumulation was observed in the cervical and thoracic cords corresponding to T2-hyperintensity lesions (Fig. 4E). None of the examinations identified any neoplasms. These findings taken together indicated a diagnosis of myelitis with GFAP-A. He was treated with two courses of intravenous methylprednisolone pulse therapy at a dose of 1.0 g/day for three consecutive days, followed by oral prednisolone treatment. Oral prednisolone treatment was started at a dose of 60 mg/day and then was gradually tapered. During hospitalization, he was treated with one course of intravenous immunoglobulin (IVIg) therapy (400 mg/kg/day for five consecutive days). His spastic paraplegia and gait disturbance gradually improved. About 5 months after starting the corticosteroid treatment and with its dose reduced to 10 mg/day, he could walk with a cane. At that time, we performed CSF examinations again. The CSF cell counts and protein concentrations were normal, and CSF GFAP-IgG was not detected. The MRI T2-hyperintensity lesions of the spinal cord also showed an improvement (Fig. 4C, D).

## Discussion

We herein report a patient with GFAP-A who presented with myelitis that slowly progressed over the course of about half a year. Previous reports describe GFAP-A patients presenting with one or more symptoms of meningitis (headache and neck pain), encephalitis (delirium, tremor, seizures, or psychiatric symptoms), and myelitis (sensory symptoms and weakness) (1, 2). These symptoms commonly have an acute or subacute onset and the frequency of onset occurring in <8 weeks was reported to be 71% in GFAP-A (2). However, some GFAP-A patients show a slow, progressive clinical course and have a long delay between symptom onset and hospital admission (5). Sechi et al. reported the characteristic features of 13 patients with GFAP-A-related myelitis and compared them with those of 41 AQP4-IgG-related myelitis patients (6). The median time to myelitis nadir was 90 days (range: 10-150 days) in patients with GFAP-A-related myelitis and it was significantly longer than that in patients with AQP4-IgG-related myelitis (median; 8 days, range; 2-63 days,  $p<0.01$ ). Although the reason for this is unclear, GFAP-A-related myelitis develops more insidiously than AQP4-IgG-related myelitis.



Our patient's spinal cord MRI showed LESCLs extending from the cervical to the thoracic cords. A previous report described the myelitis component of GFAP-A to be generally associated with LESCLs, in a similar way to that typically encountered in AQP4-IgG-related myelitis. In addition, GFAP-A-related LESCLs have been described to be more subtle with poorly defined margins and with less cord swelling compared with AQP4-IgG-related LESCLs (2, 6). Our patient's LESCLs were consistent with these previous reports. We suggest that it is important to distinguish GFAP-A from AQP4- and MOG-IgG-negative myelitis with LESCLs and these radiological characteristics.

In this study, FDG accumulation was observed in the cervical and thoracic cords corresponding to T2-hyperintensity lesions. PET imaging of GFAP-A may sometimes reveal hypermetabolism corresponding to areas of abnormality on MRI. We are aware of five reports describing brain or spinal cord FDG-PET imaging in patients with GFAP-A (7-11). Three patients, including one spinal cord-imaged patient, revealed hypermetabolism (7-9). Spinal cord FDG-PET hypermetabolism has also been reported in patients with neoplastic myelopathy, neurosarcoid myelopathy, and nonsarcoid inflammatory myelopathy (12, 13). Our findings suggest that GFAP-A may cause spinal cord FDG-PET hypermetabolism.

On neurological examination, our patient presented with spastic paraplegia. Spastic tetraplegia has been recently reported in a GFAP-A patient, although this case report demonstrated an acute presentation (14). Spasticity/hyperreflexia was reported in 62% of patients with GFAP-A-related myelitis (6). The axial MRI images of our patient's spinal cord showed T2-hyperintensity lesions of the lateral columns bilaterally. Spinal cord MRI showing T2 hyperintensity and post-gadolinium enhancement of the lateral columns has been described for GFAP-A (7, 15). We speculate that the lateral columns might be a frequently affected region and the origin of spasticity in GFAP-A-related myelitis.

Our patient visited a local hospital suffering from fever, headache, loss of appetite, weight loss, and disorientation about 22 months before admission to our hospital. Although these symptoms disappeared over three months without treatment, 19 months later, extended cerebral white matter hyperintensity lesions appeared on brain MRI. There is a possibility that this episode and the abnormal brain MRI findings may be associated with GFAP-A.

In summary, we herein described a patient with slowly progressive myelitis with LESCLs. This case highlights the importance of testing for CSF GFAP-IgG in patients with slowly progressive myelitis and LESCLs of unknown etiology, who could potentially benefit from immunotherapy.

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

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## References

1. Fang B, McKeon A, Hinson SR, et al. Autoimmune glial fibrillary acidic protein astrocytopathy: a novel meningoencephalomyelitis. *JAMA Neurol* **73**: 1297-1307, 2016.
2. Flanagan EP, Hinson SR, Lennon VA, et al. Glial fibrillary acidic protein immunoglobulin G as biomarker of autoimmune astrocytopathy: analysis of 102 patients. *Ann Neurol* **81**: 298-309, 2017.
3. Kimura A, Takekoshi A, Yoshikura N, Hayashi Y, Shimohata T. Clinical characteristics of autoimmune GFAP astrocytopathy. *J Neuroimmunol* **332**: 91-98, 2019.
4. Kunchok A, Zekeridou A, McKeon A. Autoimmune glial fibrillary acidic protein astrocytopathy. *Curr Opin Neurol* **32**: 452-458, 2019.
5. Iorio R, Damato V, Evoli A, et al. Clinical and immunological characteristics of the spectrum of GFAP autoimmunity: a case series of 22 patients. *J Neurol Neurosurg Psychiatry* **89**: 138-146, 2018.
6. Sechi E, Morris PP, McKeon A, et al. Glial fibrillary acidic protein IgG related myelitis: characterisation and comparison with aquaporin-4-IgG myelitis. *J Neurol Neurosurg Psychiatry* **90**: 488-490, 2019.
7. Dubey D, Hinson SR, Jolliffe EA, et al. Autoimmune GFAP astrocytopathy: prospective evaluation of 90 patients in 1 year. *J Neuroimmunol* **321**: 157-163, 2018.
8. Tomczak A, Su E, Tugizova M, et al. A case of GFAP-astroglial autoimmunity presenting with reversible parkinsonism. *Mult Scler Relat Disord* **39**: 101900, 2019.
9. Long Y, Liang J, Xu H, et al. Autoimmune glial fibrillary acidic protein astrocytopathy in Chinese patients: a retrospective study. *Eur J Neurol* **25**: 477-483, 2018.
10. Shu Y, Long Y, Chang Y, et al. Brain immunohistopathology in a patient with autoimmune glial fibrillary acidic protein astrocytopathy. *Neuroimmunomodulation* **25**: 1-6, 2018.
11. Tokimura R, Matsuda N, Kobayashi S, Kimura A, Kanai K. Abnormal evoked potentials in autoimmune glial fibrillary acidic protein astrocytopathy. *eNeurologicalSci* **18**: 100229, 2020.
12. Bolat S, Berding G, Dengler R, Stangel M, Trebst C. Fluorodeoxyglucose positron emission tomography (FDG-PET) is useful in the diagnosis of neurosarcoidosis. *J Neurol Sci* **287**: 257-259, 2009.
13. Flanagan EP, Hunt CH, Lowe V, et al. [(18)F]-fluorodeoxyglucose-positron emission tomography in patients with active myelopathy. *Mayo Clin Proc* **88**: 1204-1212, 2013.
14. Ip B, Lam C, Ip V, et al. Autoimmune glial fibrillary acidic protein astrocytopathy associated meningoencephalomyelitis and bilateral sensorineuronal deafness. *Mult Scler Relat Disord* **40**: 101922, 2019.
15. Allen A, Gulhar S, Haidari R, et al. Autoimmune glial fibrillary acidic protein astrocytopathy resulting in treatment-refractory flaccid paralysis. *Mult Scler Relat Disord* **39**: 101924, 2020.

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