**Submitted manuscript**

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**Title**

# A case of autoimmune glial fibrillary acidic protein astrocytopathy with excessive startle response and cortical hyperexcitability

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**Running title**:

GFAP astrocytopathy with startle response.

## Ethics statement

Informed consent for publication was obtained from the patient. The study was conducted according to the Declaration of Helsinki.

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**Abstract**

We herein report a 60-year-old man with autoimmune glial fibrillary acidic protein astrocytopathy (GFAP-A) with excessive startle response, or hyperekplexia. Short-latency somatosensory evoked potentials (SSEPs) revealed high-amplitude potentials of the early cortical component. Anti-GFAPα antibodies in the spinal fluid were positive. The hyperekplexia, other clinical symptoms, and SSEP abnormalities were resolved by corticosteroid therapy. The present case demonstrates that excessive startle response can be associated with GFAP-A, and its pathophysiology may be cortical hyperexcitability due to encephalitis.

**Keywords**:

Glial fibrillary acidic protein, Startle response, Hyperekplexia, Cortical Excitability, Somatosensory evoked potentials.



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## Introduction

Autoimmune glial fibrillary acidic protein astrocytopathy (GFAP-A) is frequently associated with movement abnormalities (85%) [1, 2]. A recent study also reported that a generalized excessive startle response, or hyperekplexia, is also seen in a non-negligible number of cases (41%) [3-5], but its pathophysiology is not well understood. We herein report a case of GFAP-A with an excessive startle response on initial examination, which is accompanied by abnormal electrophysiological findings suggesting cortical hyperexcitability, both clinical and electrophysiological abnormality improved with treatment.

## Case Report

A 60-year-old man presented to the emergency department with headache, fever, urinary retention and gait disturbance. Two weeks before, he had developed fever, headache, anorexia and difficulty urinating and walking. A week before, he had visited his home doctor, who had inserted a urinary catheter for his urinary retention. His gait disturbance worsened and he was unable to walk.

On presentation, the patient had fever (37.7°C), hypotension (96/64 mmHg) and sinus tachycardia (112 bpm). The patient was alert and well-oriented, but had reduced attention capacity. The neurological examination revealed mild tingling sensations in the extremities, a



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mild postural tremor in the fingers, hyperactive tendon reflexes in all extremities, pathological reflexes in both lower extremities, ataxia in all extremities, standing disturbance, ataxic gait, catheter-dependent urinary drainage, and orthostatic hypotension. Of note, hammer strikes to examine the tendon reflexes induced a generalized excessive startle response.

Initial blood tests revealed hyponatremia (135 mEq/L). Cerebrospinal fluid (CSF) testing showed an elevation in cell count (37 /μL, 1 neutrophil:36 lymphocytes), protein (261.5 mg/dL), and adenosine deaminase (10.8 IU/L). Head MRI revealed scattered T2WI/FLAIR high-signal changes in the basal ganglia (Figure A1). Contrast-enhanced MRI showed a linear perivascular contrast radiating from the lateral ventricular walls and lesions in the cerebellar brainstem area (Figure A2–3). Short-latency somatosensory evoked potentials (SSEPs) revealed an N20/P25 amplitude of 10.1 μV, which is consistent with the range classified as a giant SEP based on a previous study using similar recording conditions (Figure A4) [6].

The clinical findings were highly suggestive of GFAP-A. Treatment with two courses of methylprednisolone was effective, enabling the removal of the urinary catheter and recovery of walking ability. Subsequently, the patient received one course of methylprednisolone half-



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pulse therapy, followed by oral prednisolone (30 mg/day; body weight 60 kg). 6 weeks after the initial treatment, a brain MRI confirmed the disappearance of any abnormality (Figure B1–3). Consistent with a reduced excessive startle response, the giant SEP also disappeared (3.4 μV, Figure B4).

Additional tests on admission revealed positivity for anti-GFAPα antibodies in the spinal fluid (cell-based binding assay and immunostaining of frozen sections of rat brain). Antinuclear, AQP-4, MOG, TPO, Tg, and GAD1 antibodies were negative, as was the EUROLINE® paraneoplastic neurologic syndromes 12 Ag panel test (Euroimmun, Lübeck, Germany). Oligoclonal band was also negative. The diagnosis of GFAP-A was confirmed on the basis of clinical symptoms, imaging and positive anti-GFAPα antibodies in the CSF.

Prednisolone monotherapy was continued with a tapering dose and discontinued after 6 months. The residual mild gait disturbance and ataxia completely resolved. There was no recurrence of symptoms at follow-up.

## Discussion

The physiological basis of excessive startle response, or hyperekplexia, remains unclear. While the caudal brainstem is suggested as the source of excessive startle response [7], there



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is also evidence for cortical involvement [8]. In some cases of excessive startle response, giant SSEPs have been observed, suggesting the contribution of cortical hyperexcitability [8]. However, it is also suggest that cortical hyperexcitability may play a supporting role rather than a direct cause [8]. Although the present case has shown an association between cortical hyperexcitability and excessive startle response, the causal relationship between the two remains elusive.

In conclusion, we describe the SSEP findings in a case of GFAP-A with excessive startle response. Giant SEPs or cortical hyperexcitability may be associated with the pathophysiology of excessive startle response in GFAP-A. The findings of the SSEP would contribute to the diagnosis and evaluation of the pathophysiology of GFAP-A.

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**Declaration of Conflict of Interest**

The authors declare no conflict of interest regarding this manuscript.

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## Legends

**Figure.** Improvement in imaging and physiological test findings before and after treatment. **A1-3, B1-3:** Head magnetic resonance imaging (MRI) was studied before (**A1-3**: day 0) and after (**B1-3**: 6 weeks) steroid treatment. FLAIR images (**A1**, **B1**), contrast-enhanced T1 weighted axial (**A2**, **B2**) and sagittal (**A3**, **B3**) images are shown. **A4, B4:** Short latency somatosensory evoked potentials (SSEPs) were studied before (**A4**: day 0) and after (**B4**: 6 weeks) steroid treatment. We undertook two SSEP trials for each study, and N20/P25 was evaluated with the larger one of these trials. The SSEPs were induced by stimulation of the right median nerve at the wrist with an intensity of 120% of the movement threshold. The stimulation was delivered by 0.2 msec pulses at 3 Hz, and the recording settings were as follows: bandpass filter, 5–3 kHz; average sweeps, 500 stim; and analysis time, 100 msec. Ag/AgCl disk electrodes were placed at C3' (2 cm posterior to C3), C4' (2 cm posterior to C4), Fz, right Erb's point (EP), left EP, and the C5 cervical spinous process (C5S). The montage consisted of C3'–Fz (Ch1), C4'–Fz (Ch2), C5S–left EP (Ch3), and right EP–left EP (Ch4). EPi, ipsilateral Erb's point; EPc, contralateral Erb's point.



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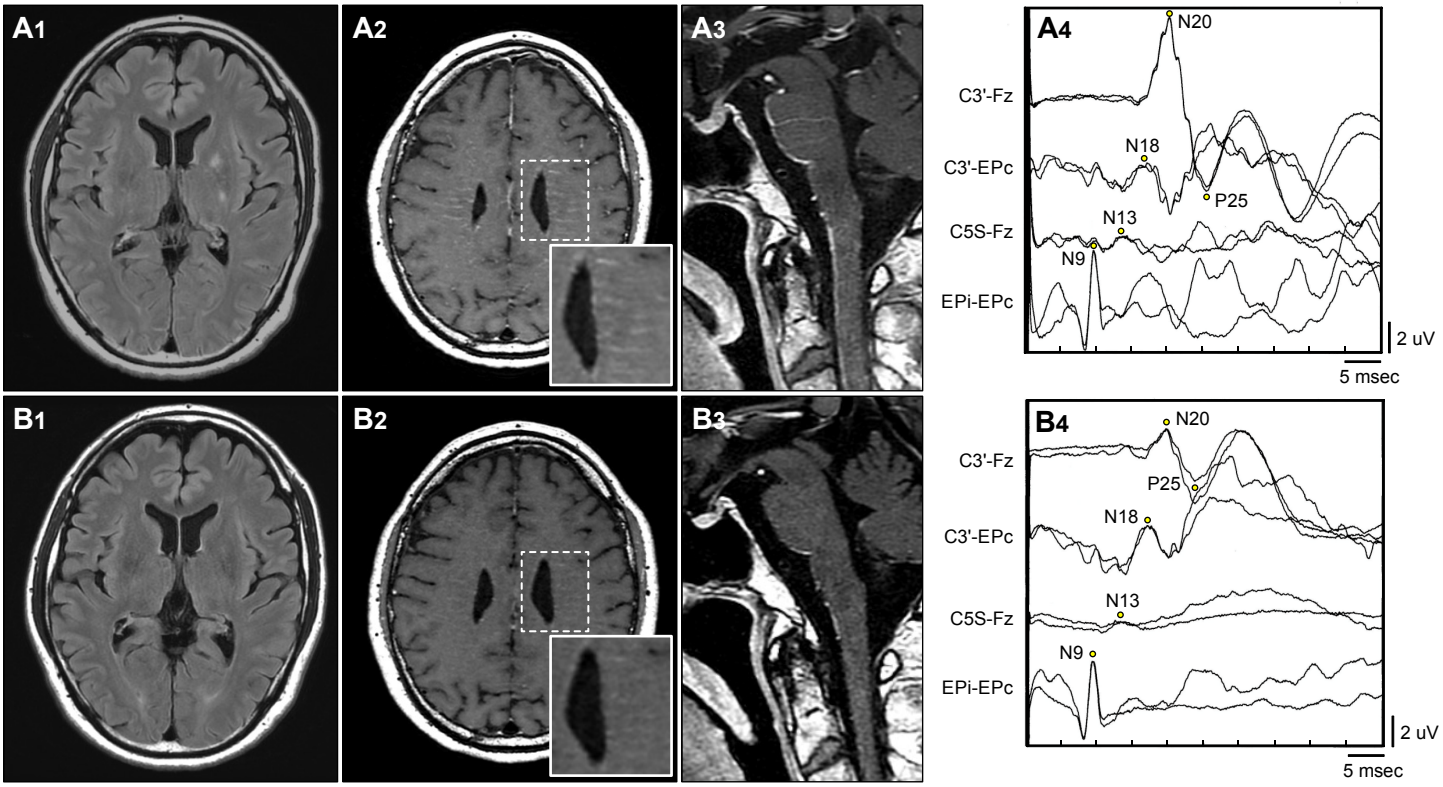
A1
A2
A3
A4
N20
C3'-Fz
N18
C3'-EPc
P25
N13
C5S-Fz
N9
EPi-EPc
2 uV
5 msec
B1
B2
B3
B4
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C3'-Fz
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