

Case Report

Autoimmune autonomic ganglionopathy in a pediatric patient presenting with acute encephalitis

Ichiro Kuki^{a,*}, Hisashi Kawawaki^a, Shin Okazaki^a, Yuka Hattori^a, Asako Horino^a,
Osamu Higuchi^b, Shunya Nakane^b^a Department of Pediatric Neurology, Osaka City General Hospital, Osaka, Japan^b Department of Clinical Research, Nagasaki Kawatana Medical Center, Nagasaki, Japan

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Abstract

Autoimmune autonomic ganglionopathy (AAG) is an acquired immune-mediated disorder that leads to systemic autonomic failure. Autoantibodies to the ganglionic nicotinic acetylcholine receptor (gAChR) are detected in 50% of AAG patients. We report the first pediatric case of AAG presenting with acute encephalitis. The patient was a 13-year-old boy who presented with orthostatic hypotension, followed by rapidly progressing disturbance of consciousness. Cerebrospinal fluid analysis revealed significant pleocytosis and increased neopterin concentration. Head MRI showed hyperintensities in bilateral caudate nuclei, putamen, hippocampus, and insula cortex. Severe autonomic dysfunctions such as severe orthostatic hypotension, bradycardia, dysuria, prolonged constipation and vomiting appeared. These symptoms were successfully controlled by repeated immunomodulating therapy with intravenous methylprednisolone pulse therapy and intravenous immunoglobulin. Autoantibodies to the $\alpha 3$ subunit of gAChR were detected at neurological onset, but were undetectable five months later. This observation indicates that AAG should be suspected in patients manifesting acute encephalitis characterized by preceding and prolonged autonomic symptoms, and immunomodulating therapy from an early stage can be effective.

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1. Introduction

Autoimmune autonomic ganglionopathy (AAG) is an acquired immune-mediated disorder that leads to systemic autonomic failure [1,2]. This disorder belongs to the category of primary autonomic neuropathy, and autoantibodies to the ganglionic nicotinic acetylcholine receptor (gAChR) are detected in some patients. The gAChRs mediate fast synaptic transmission in peripheral autonomic ganglia in the peripheral

Abbreviations: AAG, autoimmune autonomic ganglionopathy; gAChR, ganglionic nicotinic acetylcholine receptor; OH, orthostatic hypotension; IVMP, intravenous methylprednisolone pulse therapy; IVIg, intravenous immunoglobulin.

* Corresponding author at: Department of Pediatric Neurology, Osaka City General Hospital, 2-13-22 Miyakojimahondori, Miyakojima-ku, Osaka 534-0021, Japan. Tel.: +81 6 929 1221; fax: +81 6 929 1091.

E-mail address: gpkichiro0926@yahoo.co.jp (I. Kuki).

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autonomic nervous system [3]. However, the role of these autoantibodies and the clinical effects on the central nervous system remain unknown. We report the first pediatric case of AAG presenting with acute encephalitis accompanied by detectable levels of autoantibodies to the $\alpha 3$ subunit of gAChR (anti-gAChR $\alpha 3$), which was successfully controlled by immunomodulating therapy.

2. Case report

The patient was a 13-year-old boy who had no remarkable medical or family history. After two days of high-grade fever, the patient presented to a local hospital with orthostatic hypotension (OH) (Supplemental Fig. 1), and then disturbance of consciousness progressed rapidly. The patient was transferred to our hospital one day after onset of neurological symptoms. Intubation and mechanical ventilation were required due to severe dyspnea and disturbance of consciousness with a Glasgow Coma Scale score of 9. Head MRI including diffusion-weighted imaging showed normal findings, but an electroencephalogram demonstrated widespread high voltage slow waves dominant in bilateral frontal areas without epileptic discharge. Cerebrospinal fluid (CSF) analysis revealed significant pleocytosis (cells 49/ μ L; normal range, <5/ μ L) and increase in protein (68 mg/dl; normal range, <45 mg/dl), myelin basic protein (124.0 pg/ml; normal range, <102.0 pg/ml) and neopterin concentration (836 ng/ml; normal range, <20 ng/ml), which strongly suggested acute encephalitis. The CSF was negative for oligoclonal band and normal for glucose and lactate. Treatment was initiated with intravenous immunoglobulin (IVIg, 400 mg/kg over 5 days) and intravenous methylprednisolone pulse therapy (IVMP, 30 mg/kg over 3 days). To protect his cerebral function, brain hypothermia therapy was performed with edaravone and levetiracetam under continuous thiopental sodium infusion.

On the fifth day, improved consciousness with a Glasgow Coma Scale score of 14 allowed extubation, but chronic autonomic dysfunction persisted. The patient was treated with bed rest and prescribed midodrine for severe OH and sinus bradycardia (minimum heart rate during sleep, 38 bpm) (Supplemental Fig. 1). Urinary catheterization was required due to dysuria. Total parenteral nutrition and regular enema was required due to chronic constipation and vomiting. Serum noradrenaline (0.03 ng/ml; normal range, 0.10 < ng/ml) level was significantly low. 123 I-MIBG myocardial scintigraphy revealed a normal heart/mediastinum ratio, and peripheral motor and sensory nerve conduction study was within normal range for the patient's age. Head MRI performed two weeks after the onset of symptoms revealed hyperintensities in bilateral caudate nuclei, putamen, hippocampus, and insula cortex (Fig. 1A–C). Cerebral blood flow assessment by

single photon emission computed tomographic (SPECT) showed decreased uptake in left frontal and temporal areas, and benzodiazepine receptor imaging by SPECT showed decreased uptake in left frontal area.

Repeated immunomodulating therapies (IVIg twice, IVMP four times, and prednisolone for 4 months in total) resulted in recovery. At one month, the patient was able to speak, walk, and eat by himself. Head MRI was conducted 3 weeks after and showed normal (Fig. 1D–F). At two months, findings of electroencephalogram, SPECT, and serum catecholamine levels returned to normal and head 18 F FDG-PET results were normal. Whole-body enhanced CT and 18 F FDG-PET showed no cancer lesions. At three months after onset, the patient was discharged from the hospital with only mild OH (Fig. 1).

Virological studies of nasopharyngeal aspirates, stool, and blood were negative. Metabolic analyses of serum and urine acyl carnitine profiles, organic acid profiles, and aminograms showed normal profiles. Anti-nuclear antibody, anti-double-stranded DNA antibody, anti-thyroid peroxidase antibody, anti-thyroglobulin antibody and thyroid stimulating hormone receptor antibody, anti-N-methyl-D-aspartate receptor antibody tested by a cell-based assay and anti-glutamic acid decarboxylase antibody were negative, but other antibodies were not examined. Repeated tests of anti-streptolysin O antibody and anti-streptokinase antibody were not significantly increased. Anti-gAChR $\alpha 3$ antibodies in serum were detected by the luciferase immunoprecipitation systems (LIPS). The initial test conducted at admission was positive at a level of 1.58 antibody index (A.I.) (normal range of A.I. = 1.000>), and the level dropped to 1.31 A.I. one month after onset of symptoms. Thereafter, the antibodies were undetectable during the subsequent five months.

3. Discussion

This is the first report of a pediatric case of AAG presenting with acute encephalitis accompanied by anti-gAChR $\alpha 3$ antibody. The possibility of AAG should be considered in cases of acute encephalitis characterized by preceding and prolonged autonomic symptoms, and immunomodulating therapy from an early stage can be effective. In the present case, we detected the anti-gAChR $\alpha 3$ antibodies using LIPS, which is a powerful diagnostic technique for the serological testing of antibodies that are associated with many different human pathogens, especially with subunit-specific antibodies [2].

Nearly all previous reports of anti-gAChR positive AAG are adult cases. In patients with AAG, the major clinical symptoms are those of autonomic dysfunction, including OH, abnormal perspiration, dysuria, and constipation. Only one reported adult case manifested late-onset encephalopathy, and was successfully treated

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