症例報告

OPSOCLONUS-MYOCLONUS-ATAXIA SYNDROME AFTER ADRENOCORTICOTROPIC HORMONE THERAPY FOR INFANTILE SPASMS IN A BOY WITH DOWN SYNDROME

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Abstract

Introduction: Opsoclonus-myoclonus-ataxia syndrome (OMAS) is a rare acquired autoimmune paraneoplastic movement disorder associated with neuroblastoma. Additionally, autoimmune diseases and infantile spasms are common comorbidities of Down syndrome (DS).

Case report: A boy aged 1 year and 9 months with DS suffered from anti-seizure drug-resistant infantile spasms. We administered low-dose adrenocorticotropic hormone (ACTH; 0.0125 mg/kg/day) for 14 days, and the infantile spasms disappeared; however, he presented with limb myoclonus and involuntary conjugate multidirectional saccadic eye movements on day 3 after the end of ACTH therapy. OMAS was suspected and a complete workup was performed. No tumors, including neuroblastoma, were detected. Antibodies against glutamic acid decarboxylase 65 and Tr/Delta/Notch-like epidermal growth factor-related receptor were found. Two courses of intravenous methylprednisolone pulse therapy (30 mg/kg/day for three consecutive days), oral prednisolone (PSL) treatment (2 mg/kg/day for four consecutive days), and intravenous immunoglobulin treatment (2g/kg/3days) were administered. OMAS symptoms resolved, and PSL tapering was initiated on day 17 after the start of immunomodulatory therapy.

Conclusion: We present the case of a patient with DS who developed OMAS after ACTH therapy for infantile spasms. Paraneoplastic syndrome-associated antibody testing facilitated the early diagnosis of OMAS. The development of autoimmune diseases should be considered when ACTH therapy is used for DS.

Key words: adrenocorticotropic hormone, Down syndrome , glutamic acid decarboxylase, opsoclonus-myoclonus-ataxia syndrome, Tr/Delta/Notch-like epidermal growth factor-related receptor,

1. Introduction

Opsoclonus-myoclonus-ataxia syndrome (OMAS) is an autoimmune disorder characterized by involuntary eye movements, multifocal myoclonus, and ataxia. This disorder occurs primarily in young children but can develop at any age. In children, OMAS often occurs as a paraneoplastic

syndrome with neuroblastoma and related tumors. Nonetheless, paraneoplastic syndrome-related antibodies (PNSA) are rarely detected. Although OMAS is thought to be associated with the activation of autoreactive T-cells, B-cell activation and antigen presentation are important contributors to its pathophysiology, and autoantibody-mediated autoimmunity may be involved in some OMAS cases [1) 2)]. The primary treatment for OMAS is a combination of adrenocorticotropic hormone (ACTH), oral steroids, or high-dose intravenous steroids with or without intravenous immunoglobulin (IVIg) [1)].

Epileptic spasm is the most frequent seizure type in individuals with Down syndrome (DS) [3)]. A typical clinical feature of DS is susceptibility to organ-specific autoimmune diseases, such as Hashimoto's thyroiditis, Graves' disease, type 1 diabetes mellitus (T1DM), celiac disease, alopecia, vitiligo, and idiopathic arthritis [4) 5)]. This study reports the case of a boy with DS who developed OMAS with PNSA after ACTH treatment for infantile spasms.

2. Case report

A boy with DS aged 1 year and 9 months was admitted to our hospital for treatment of epileptic spasms with ACTH therapy. He was born prematurely (gestational age of 32 weeks and 5 days) with a very low birth weight (1492 g) without neonatal asphyxia. There was no family history of hereditary neoplastic syndrome, autoimmune diseases, or neurological diseases. He underwent surgical treatment for patent ductus arteriosus at age 4 days and congenital duodenal atresia at age 10 days. At 11 months of age, he developed loss of smile, neck control, and roll-over and had epileptic spasms with hypsarrhythmia on interictal electroencephalogram (EEG); the final diagnosis was infantile spasms of genetic etiology.

Treatment with valproic acid and vitamin B6 did not resolve the spasms; therefore, vigabatrin (VGB) treatment was initiated but was soon discontinued because it increased myoclonic seizures and caused interstitial pneumonia, although the spasms disappeared. Additionally, VGB-associated brain abnormalities in the bilateral globus pallidum, fornix, and anterior cerebral commissures without involuntary movement were found on magnetic resonance imaging (MRI) but disappeared 4 months after VGB treatment was discontinued [6)]. Epileptic spasms with hypsarrhythmia recurred after discontinuation of VGB treatment and did not improve with clonazepam, ethosuximide, and topiramate, leading to hospital admission for ACTH therapy. He did not receive any vaccines within two months prior to the start of ACTH therapy.

We administered low-dose ACTH (0.0125 mg/kg/day; Cortrosyn Z Intramuscular Injection®; Alfresa Pharma Corporation, Osaka, Japan) for 14 days. Epileptic spasms resolved on day 5, and hypsarrhythmia on EEG resolved on day 7 after administration. However, he developed limb myoclonus and involuntary conjugate multidirectional saccadic eye movements, suggestive of opsoclonus, on day 3 after the end of ACTH therapy. The patient also presented sleep disturbances and irritability and eventually developed eating difficulties and weight loss due to orolingual dyskinesia.

We performed blood, urine, and cerebrospinal fluid (CSF) tests, chest and abdominal CT scans with contrast agents, and brain MRI. Tumors, lymph node swelling, and abnormal signals were not found on imaging. His blood and urine test results were within normal limits, and

the CSF had normal cell counts and protein levels, negative cytology, and no viral markers. Neuroblastoma markers, including serum neuron-specific enolase, vanillylmandelic acid, and homovanillic acid, were within normal limits (Table 1). However, the EUROLINE Paraneoplastic Neurologic Syndromes 12 Ag (IgG) test® (BML, Inc, Tokyo, Japan) was positive for anti-glutamic acid decarboxylase (GAD)-65 antibody and anti-Tr/Delta/Notch-like epidermal growth factor-related receptor (Anti-Tr/DNER) antibodies, which are PNSAs (Table 2). Based on these findings, we made the clinical diagnosis of OMAS.

Table 1. Laboratory findings from the onset to the start of treatment of OMAS

Blood test									Cerebrospinal fluid		
WBC	9400	/μl	CRP	1.81	mg/dl	IgA	186	mg/dl	Polynuclear cell	1	/μl
RBC	405x10⁴	/μl	TP	6.3	g/dl	IgG	902	mg/dl	Mononuclear cell	0	/μl
Hemoglobin	12.7	g/dl	Alb	3.6	g/dl	IgM	62	mg/dl	Glucose	75	mg/dl
Platelet	41.0x10⁴	/μl	AST	17	IU/l	C3	129	mg/dl	Protein	17.4	mg/dl
PT-INR	0.91		ALT	14	IU/l	C4	44	mg/dl	Albumin	80.0	μg/ml
aPTT	<23.0	sec	LDH	190	IU/l	CH50	55	CH50/ml	IgG	<1.0	mg/dl
CMV IgG	positive		CK	42	IU/l	CD4+ T cell	45.8	%	NSE	7.2	ng/ml
CMV IgM	negative		Glucose	90	mg/dl	CD8+ T cell	38.5	%	Oligoclonal band	negative	
EBV anti VCA IgG	negative		Sodium	137	mEq/l	CD4/CD8 ratio	1.19		Lactate	12.4	mg/dl
EBV anti VCA IgM	negative		Potassium	3.9	mEq/l	T cell	69.4	%	β2MG	0.7	mg/L
EBV anti EBNA IgG	negative		Chloride	103	mEq/l	B cell	17.8	%			
Mycoplasma	negative		Calcium	9.2	mg/dl	NK cell	11.8	%	Urine test		
TSH	0.88	μIU/ml	BUN	8	mg/dl	Anti nuclear antibody	negative		VMA	16.02	mg/g・Cre
fT4	1.62	ng/dl	Creatinine	0.2	mg/dl	Anti-ARS antibody	negative		HVA	18.77	mg/g・Cre
NSE	18.2	ng/ml	T-bilirubin	0.5	mg/dl	β2MG	2.0	mg/L			
VMA	12.5	ng/ml				IL-2R	549	U/ml			
HVA	20.6	ng/ml				Ferritin	44	ng/ml			

Alb: albumin, ALT: alanine aminotransferase, aPTT: activated partial thromboplastin time, ARS: aminoacyl synthetase, AST: aspartate aminotransferase, β2MG: beta-2-microglobulin, BUN: blood urea nitrogen, CD: cluster of differentiation, CH50: 50% hemolytic complement activity, CK: creatinine kinase, CMV: cytomegalovirus, CRP: C-reactive protein, EBV: Epstein-Barr virus, fT4: free tetraiodothyronine, HVA: homovanillic acid, Ig: immunoglobulin, sIL-2R: soluble interleukin-2 receptor, LDH: lactate dehydrogenase, NK: natural killer, NSE: neuron specific enolase, PT-INR: prothrombin time and international normalized ratio, RBC: red blood cell, TP: total protein, TSH: thyroid stimulatory hormone, VCA: viral capsid antigen, VMA: vanillylmandelic acid, WBC: white blood cell

Table 2. Results of paraneoplastic neurological syndrome related onconeural antibodies

Antibody	Result
Anti-amphiphysin (AMPH)	−
Anti-CV2/collapsing response mediator protein (CRMP)-5	±
Anti-paraneoplastic antigen MA2 (PNMA2)	−
Anti-Ri	±
Anti-Hu	−
Anti-Yo	−
Anti-recoverin	−
Anti-SRY-Related HMG-Box Gene 1 (SOX1)	−
Anti-titin	±
Anti-zic4	−
Anti-glutamic acid decarboxylase 65 (GAD65)	+++
Anti-Tr/anti-Delta/Notch-like epidermal growth factor-related receptor (Tr/DNER)	+

−: negative, ±: borderline, + and ++: positive, +++: strong positive

Two courses of intravenous methylprednisolone (mPSL) pulse therapy (30 mg/kg/day for three consecutive days), oral PSL treatment (2 mg/kg/day for four consecutive days), and IVIg treatment (2g/kg/3days) were administered. During treatment, opsoclonus, leg myoclonus, and oral involuntary movements decreased, and the patient was able to eat.

On the 12th day after the start of immunomodulatory therapy, sleep disturbances improved, opsoclonus disappeared, and the patient was able to gaze. On the 17th day, steroid tapering was initiated, and the patient could roll over without symptom recurrence. An EEG showed no hypsarrhythmia. Six months later, PSL was tapered without recurrence of OMAS-associated symptoms. Additionally, anti-GAD65 and anti-Tr/DNER antibodies remained positive without malignancy.

3. Discussion

OMAS is a rare acquired autoimmune movement disorder. A national retrospective study in Japan and a prospective study in the United Kingdom reported that the estimated incidence of OMAS in these countries was 0.18 – 0.40 cases per million [7) 8)]. The median age at onset was 16.5 months, and the most common causes in Japan were neuroblastoma (43.5%), infections (39.1%), and vaccinations (8.7%) [7)].

In the present case, OMAS was not associated with neuroblastoma, infections, or vaccinations; however, the patient met three of the four clinical diagnostic criteria for OMAS: (1) opsoclonus or ocular flutter; (2) presence of myoclonus or ataxia; and (3) behavioral or sleep disturbance, often with marked irritability [1)]. The diagnosis of acute cerebellar ataxia, acute infectious meningoencephalitis, brain structural abnormalities in the pons and/or cerebellum, liver disease, and drug intoxication was negative.

The suggested mechanism underlying OMAS is paraneoplastic immune-mediated encephalopathy; however, the disease pathogenesis remains unclear [7)]. Elevations of neopterin [9)], B-cell activating factor belonging to the tumor necrosis factor family, C-X-C motif chemokine ligand 13, oligoclonal bands associated with B-cell activity [10)], CC chemokine ligand (CCL)17, CCL19, CCL21, and CCL22 associated with T-cell activity [11) 12)], and microglial activation have been reported in the CSF of patients with OMAS [13)]. These assays can help monitor disease activity, despite their low sensitivity and specificity [1)]. The number of CD4 + helper T-cells is lower than that of CD8+ cytotoxic T-cells immediately after ACTH therapy [14)]. In addition, DS is clinically characterized by susceptibility to organ-specific autoimmune diseases, including Hashimoto's thyroiditis, Graves' disease, T1DM, celiac disease, alopecia, vitiligo, and idiopathic arthritis. Nonetheless, the role of anti-GAD65 and anti-Tr/DNER antibodies in DS is unclear [4) 5)].

In the present case, the levels of nonspecific inflammatory markers, including C-reactive protein, C4, 50% hemolytic complement activity, soluble interleukin-2 receptor, and beta-2-microglobulin (β2MG), increased slightly; nonetheless, the $CD4^+$ to $CD8^+$ T-cell ratio and markers of neuroblastoma in the blood were normal. Furthermore, there were no abnormalities in cell count, IgG, β2MG, and oligoclonal bands in the CSF. In contrast, two paraneoplastic neurological syndrome-related onconeural antibodies—anti-GAD65 and anti-Tr/DNER antibodies—were detected in the blood.

Autoantibodies against Ri, Hu, Yo, Ma1, Ma2, N-methyl-D-aspartate receptor, and neurofilaments are associated with paraneoplastic OMAS [15]. In children with OMAS, the analysis of type 1 antineuronal nuclear antibodies and paraneoplastic autoantibody panels is recommended as the initial workup[1) 16)].

GAD65 is an intracellular enzyme present in the pancreas and central nervous system that converts glutamate into γ -aminobutyric acid (GABA), a major inhibitory neurotransmitter [17) 18)]. Sixty-six percent of GAD65 antibody-positive patients present with neurological disorders such as stiff-person spectrum disorders, cerebellar ataxia, epilepsy, limbic encephalitis, and secondary manifestations, including myelopathy, brainstem dysfunction, and cognitive impairment, and 11% with non-neurological presentations (e.g., GAD65 antibody detected as part of T1DM evaluations) [19].

Anti-Tr/DNER antibodies are neuronal cell surface antigen antibodies against DNER expressed on the surface of cerebellar Purkinje cells. These antibodies are found mainly in adult males who develop Hodgkin lymphoma. Most anti-Tr/DNER antibody-positive patients present with cerebellar ataxia; nonetheless, extracerebellar signs are rare [20]. The mechanism of opsoclonus (random, chaotic, continuous saccadic eye movements occurring in all directions) is hypothesized to be saccadic oscillations resulting from pause cell dysfunction in the paramedian pontine reticular formation in the brainstem, which affects the suppression of burst cells and destabilizes horizontal and vertical saccade pulse generators [21].

Various autoantibodies have been detected in paraneoplastic OMAS[15], including anti-GAD antibodies, but no anti-Tr/DNER antibodies have been reported to the best of our knowledge[22]. Although the role of anti-GAD65 and anti-Tr/DNER antibodies in OMAS is unclear, we speculate that opsoclonus, myoclonus, oral dyskinesia, sleep disturbance, irritability, emotional disorders, and cerebellar ataxia are associated with these antibodies. ACTH, unlike prednisolone, has been reported to have an anti-inflammatory effect through a glucocorticoid-dependent mechanism and a glucocorticoid-independent mechanism through melanocortin.[23] However, our case was not sufficient to clarify the pathogenesis of the production of PNSAs after ACTH therapy, which is also administered as a treatment for OMAS. We speculated that the immunomodulators interacted with DS, which is frequently affected by autoimmune disease, to produce PNSAs.

Treatment should be effective within 30 weeks of onset to prevent serious neurological outcomes [7]. In this case, OMAS appeared after the completion of ACTH therapy, allowing for early diagnosis and therapeutic intervention. After diagnosis, immunomodulatory therapy with mPSL pulse therapy and IVIG was introduced. OMAS-related symptoms disappeared, and steroid treatment was tapered. PNSAs may appear before tumors; thus, OMAS recurrence and tumor appearance should be closely monitored.

This study has a limitation. Exclusion diagnosis does not rule out the possibility of forced normalization of epilepsy, a psychiatric symptom that occurs after refractory seizures are controlled and epileptic activities are decreased. Forced normalization is more common in female patients, appearing at a median age of 28.3 ± 14.2 years, and is rare in children [24]. In our case, steroid pulse therapy was effective, and there was no recurrence of seizures after symptom resolution; therefore, the possibility of forced normalization was unlikely.

In conclusion, we presented the case of a patient with DS who developed OMAS after ACTH therapy for infantile spasms. The detection of PNSAs anti-GAD65 and anti-Tr/DNER antibodies allowed for the implementation of a treatment strategy. Clinicians should be aware of the potential development of autoimmune diseases after ACTH therapy for infantile spasms with DS.

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Informed consent

The patient's parents gave verbal informed consent for the publication.

Conflict of Interest Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this study.

Author contributions

Takafumi SAKAKIBARA organized and coordinated the trial. Ayaka OHARA (chief investigator), Takafumi SAKAKIBARA, Yoko TAKEDA, and Atsushi INAGAKI analyzed the data. SAKAKIBARA, Yoko TAKEDA, Atsushi INAGAKI, and Keiji NOGAMI designed the trial. All authors wrote the final manuscript and met the ICMJE authorship criteria.

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