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Original article

Long-term outcome of a group of Japanese children with myelin-oligodendrocyte glycoprotein encephalomyelitis without preventive immunosuppressive therapy

Naomi Hino-Fukuyo [a,*], Kazuhiro Haginoya [a], Toshiyuki Takahashi [b,c], Ichiro Nakashima [b,d], Kazuo Fujihara [b], Yoshiki Takai [b], Manami Akasaka [e], Shigeo Kure [a]

[a] Department of Pediatrics, Tohoku University School of Medicine, Sendai, Japan
[b] Department of Neurology, Tohoku University of School of Medicine, Sendai, Japan
[c] Department of Neurology, National Hospital Organization Yonezawa Hospital, Yamagata, Japan
[d] Department of Neurology, Tohoku Medical and Pharmaceutical University, Sendai, Japan
[e] Department of Pediatrics, Iwate Medical University, Morioka, Japan

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Abstract

Introduction: There is increasing evidence that immunosuppressive therapy is essential for reducing disease activity and avoiding further attacks in patients positive for anti-myelin-oligodendrocyte glycoprotein (MOG) antibodies. However, to date, no placebo-controlled trial has been published.

Objective: We aimed to evaluate the long-term outcome and anti-MOG antibody titers of seropositive Japanese pediatric patients without long-term immunosuppressive therapy.

Methods: Of 11 consecutive patients positive for anti-MOG antibodies seen at Tohoku University Hospital from 1992 to 2013, 5 patients did not receive preventive long-term immunosuppressive treatment and had been followed up longitudinally (more than 60 months).

Results: The follow-up periods were 68–322 months (median, 150 months). The expanded disability status scale scores of all patients were 0 at the last observation. Three patients were negative for the antibody at the last follow-up, and the titers of the two patients whose anti-MOG antibodies were positive at the last follow-up were lower than at the first examinations. The interval to the second attack in three patients was 1–124 months (median, 33 months). Acute attacks were treated with methylprednisolone pulse therapy (four patients) or intravenous immunoglobulin (one patient). All patients achieved full recovery after acute therapy. Oral corticosteroid was tapered over a period of 6–26 weeks (median, 17 weeks).

Conclusions: We reported our experience with very long-term follow-up of 5 Japanese pediatric patients with anti-MOG antibody-positive disease who did not receive long-term immunosuppressive therapy. Persistent positivity to anti-MOG antibody in some patients suggests the necessity for long-term follow up despite infrequent relapse.

Keywords: Anti-myelin-oligodendrocyte glycoprotein (MOG) antibody; Acute disseminated encephalomyelitis (ADEM); Optic neuritis (ON); Multiphasic disseminated encephalomyelitis (MDEM); Preventive immunosuppressive therapy; Long-term outcome

* Corresponding author at: Department of Pediatrics, Tohoku University School of Medicine, 1-1 Seiryo-machi Aoba-ku, Sendai 980-8574, Japan.
E-mail address: naomi-h@zc4.so-net.ne.jp (N. Hino-Fukuyo).

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1. Introduction

Anti-myelin-oligodendrocyte glycoprotein (MOG) antibody disease is the newest entity on the growing list of antigen-specific autoimmune diseases of the central nervous system (CNS). Anti MOG-antibodies have been reported in ~40% of children at first presentation of an acquired demyelinating syndrome [1]. Anti-MOG antibodies are present in patients with acute disseminated encephalomyelitis (ADEM), aquaporin-4 (AQP4) antibody-negative neuromyelitis optica spectrum disorders (NMOSD), isolated optic neuritis (ON), transverse myelitis, encephalomyelitis, and atypical multiple sclerosis (MS). These are now often referred to as MOG-IgG-associated encephalomyelitis [2]. Clinical outcomes are now generally favorable, although the treatment response to methylprednisolone pulse therapy varies [3]. There is increasing evidence that immunosuppressive therapy is essential for reducing disease activity and avoiding further attacks [4–6]. In any MOG-seropositive case, long-term immunosuppression should also be considered in the event of clinical relapse [5,6]. However, it remains unclear if long-term immunosuppressive treatment is indispensable from a risk-benefit profile standpoint in all patients with MOG-seropositivity [5], and no placebo-controlled trials have been published on this issue yet. In this study, we aimed to evaluate the long-term outcome and anti-MOG antibody titers of seropositive Japanese pediatric patients without immunosuppressive therapy.

2. Materials and Methods

2.1. Patients

11 pediatric patients who had been diagnosed with inflammatory CNS demyelinating diseases at Department of Pediatrics, Tohoku University Hospital were found positive for anti-MOG antibodies from 1992 to 2013. The expanded disability status scale scores (EDSS) of all patients were 0 at the last follow-up. We published data of three of the eleven patients in 2015 [3].

Brain magnetic resonance imaging (MRI) was performed at disease onset in all patients and spinal MRI was performed in four patients at onset. Other diseases with white matter lesions, such as vasculitis, viral encephalitis, and metabolic disorders, were excluded based on blood tests, lumbar puncture, and sequential brain MRI. The patients were finally diagnosed with ADEM, multiphasic disseminated encephalomyelitis (MDEM), meningitis and ON according to the International Pediatric Multiple Sclerosis Study Group criteria [7].

Long-term immunosuppressive treatment was defined as receiving immunosuppressive treatment more than one year after onset. Of 11, ten patients did not receive long-term immunosuppressive treatment. Of these 10 patients without long-term immunosuppressive treatment, we could obtain the samples of 5 patients after long follow-up. The other 5 patients were lost to follow-up and their samples were unavailable.

2.2. Approvals and patient consent

All the patients and the guardians provided written informed consent. This study was approved by the Ethics Committee of Tohoku University School of Medicine.

2.3. Serum samples

The first serum samples were obtained after disease onset but before therapy in four patients, and 2 year after onset of second attack in one patient (case 3). New samples were then obtained regularly at least once a years for longitudinal follow-up in two patients; samples were obtained from one patient (case 1) after relapse and from another patient (case 3) from the first examination (1 year after onset). Stored sera from the remaining three patients, collected during visits to our hospital, were analyzed retrospectively. All samples were immediately centrifuged and stored at −80 °C. All patients were assessed before any treatment or at least 1 month after intravenous methylprednisolone/intravenous immunoglobulin (IVIG).

2.4. Assay for antibody

Anti-MOG antibodies were assayed using cell-based assays with HEK-293 cells transfected with human AQP4 M23-isoform or full-length human MOG, as described previously [8,9]. The titers were calculated semi-quantitatively using consecutive two-fold end-point dilutions.

3. Results

A clinical summary and the anti-MOG antibody titers of patients are shown in Table 1. The follow-up period was 68–322 months (median, 150 months). All patients were negative for anti-AQP4 antibodies. During follow-up, no patient was diagnosed with MS or NMOSD.

Two of the five patients had only one attack, and the remaining three exhibited a relapsing course. The time to the second attack in cases 1, 3, and 4 was 1–124 months (median, 33 months). EDSS scores of all patients were 0 at the last follow-up.

The treatments administered to the patients are summarized in Table 2. Acute attacks were treated with methylprednisolone pulse therapy, but case 2 was treated only with IVIG during the acute phase. All patients

Table 1
Clinical feature of patients.

Case	gender	age of onset	symptoms at onset	diagnosis at onset	brain MRI at onset	spinal MRI at onset	relapse	clinical feature of relapse			final diagnosis	follow-up period	MOG-Ab titer	MOG-Ab titer at last follow-up	final outcome EDSS (age)
								time from first attack		symptoms of relapse					
1	M	2 y	fever, vomiting, disturbance of consciousness	meningitis	multiple WM, bil. BG (3 weeks after onset)	NL	1	124 months		bil. ON	ADEM and bil. ON	150 months	1: 65,536 (at first attack)	1: 2048	0 (15 y)
2	F	3 y	gait disturbance, disturbance of consciousness	ADEM	multiple WM	NL	0				ADEM	68 months	1: 2048 (at first attack)	1:128	0 (10 y)
3	M	5 y	fever, headache, pain of lt. eye	meningitis	NL (at first attack), rt. optic nerve (at second attack)	not done	1	33 months		rt. ON	meningitis and rt. ON	87 months	1:4096 (at one years after first attack)	negative	0 (14 y)
4	F	6 y	fever, headache	meningitis	multiple WM, bil thalami (at first and third attack), deep gray matter (at second attack)	NL	3	second attack	1 month	somnolence, gait disturbance, dysphagia	MDEM	322 months	1: 256 (at second attack)	negative	0 (33y)
								third attack	31 months	dysesthesia in the rt. foot					
								fourth attack	90 months	fever and headache					
5	M	10 y	diarrhea, headache, pain of bil. eyes, loss of vision	bil. ON	optic nerve	NL	0				bil. ON	212 months	1: 16,384 (at first attack)	negative	0 (27y)

M; male, F; female, y; years old, m; months old, MRI; magnetic resonance imaging, ON; optic neuritis, EDSS; expanded disability status scale, MOG-ab; myelin oligodendrocyte glycoprotein antibody, NL; normal, WM; white matter, bil.; bil ateral, BG; basal ganglia, lt.; left, rt.; right, ADEM; acute disseminated encephalomyelitis, MDEM; multiphasic disseminated encephalomyelitis.

Table 2
Therapy of patients.

Case	acute therapy (number of times)		duration of oral steroid tapering
1	first attack	mPSL(3)	6 weeks
	second attack	mPSL(2)	15 weeks
2	IVIG(1)		
3	first attack	no data	
	second attack	mPSL(3)	none*
4	first attack	anti-virus drugs, anti epileptic drugs	
	second attack	mPSL(1)	21 weeks
	third attack	mPSL(1)	22 weeks
	forth attack	mPSL(1)	26 weeks
5	mPSL(1)		12 weeks

mPSL; methylprednisolone pulse therapy, IVIG; intravenous immunoglobulin.
* because of renal glycosuria.

achieved full recovery after acute therapy. Oral steroid tapering was performed in all patients except for case 2; the duration of tapering was 6–26 weeks (median; 17 weeks).

The anti-MOG antibody titers of the patients in this study are summarized in Fig. 1. Three patients (cases 3, 4, and 5) became negative for anti-MOG antibodies. In case 3, samples collected during the follow-up visits were all negative. Two patients (cases 1 and 2) who were positive for anti-MOG antibodies at the last follow-up had lower titers than at the first examination.

4. Discussion

Here, we described the long-term outcome of Japanese pediatric cases with anti-MOG antibodies without preventative immunosuppressive therapy. There is no report of a follow-up study of anti-MOG antibody titer for such a very long period.

All the patients in this study had good outcome despite no long-term immunosuppressive treatment after relapses. Hacohen et al. reported no differences in patient demographics, clinical symptoms at onset, or final demyelinating phenotype between patients who were and were not treated with disease-modifying drugs [10]. The current study supports this conclusion.

Oliverira reported that no patients in their monophasic group received long-term immunosuppressive therapy after acute phase treatment; serum anti-MOG antibody levels declined spontaneously in their cohort and remained negative throughout follow-up [11]. In our series, three patients (cases 3, 4, and 5) converted to negative for anti-MOG antibodies, which is consistent with Oliverira's observation.

It is possible that the decreased anti-MOG antibody titer observed in case 2 was associated with immunoglobulin therapy during acute phase therapy. As a maintenance therapy, IVIG was associated with the greatest improvement in annualized relapse rates and EDSS scores [10]. Interestingly, in a recent study using cerebellar section cultures from transgenic mice and anti-MOG antibody-induced demyelination, treatment with IVIG protected against demyelination in a dose-dependent manner [12].

Anti-MOG antibody serum titers are significantly higher during the acute phase than the remission phase [13]. In fact, the anti-MOG antibody titers of all our patients at the last follow-up were decreased compared with at first examination during the acute phase.

In a 5-year longitudinal study of pediatric patients, Prosbtel et al. reported that those who experienced relapses had persistent fluctuations in anti-MOG antibody titers during the follow-up period [14]. It is interesting, in the current study, that case 1 remained free from relapse for nearly 10 years and case 5 had no relapse for more than 17 years, despite high anti-MOG antibody titers in the first analysis. On the other hand, case 4 had three relapses despite lower anti-MOG antibody titers than case 1 and 5.

Therefore, some patients may have relapses after 10 years from the last attack, but the antibody titers or positivity may not necessarily predict the risk of relapse.

It is still controversial whether long-term preventive immunosuppressive therapy is necessary for relapsing acquired demyelinating diseases associated with anti-MOG autoantibody. It was reported that long-term immunosuppressive therapy was associated with a reduced number of new attacks and anti-MOG antibody serum positivity [11]. Furthermore, after immunosuppressive treatment, half of the patients who were positive for anti-MOG antibodies had a seronegative result during the 2-year follow-up period [11]. Treatment with immunosuppressive drugs for at least 3 months following attack onset was associated with reduced risk of a second relapse [15]. In contrast, all the patients in the current study had good outcome despite no long-term immunosuppressive treatment. Hacohen et al. observed the higher relapse rate and poorer outcome in the group receiving more therapy and attributed this paradox to possible bias in treatment decision [10].

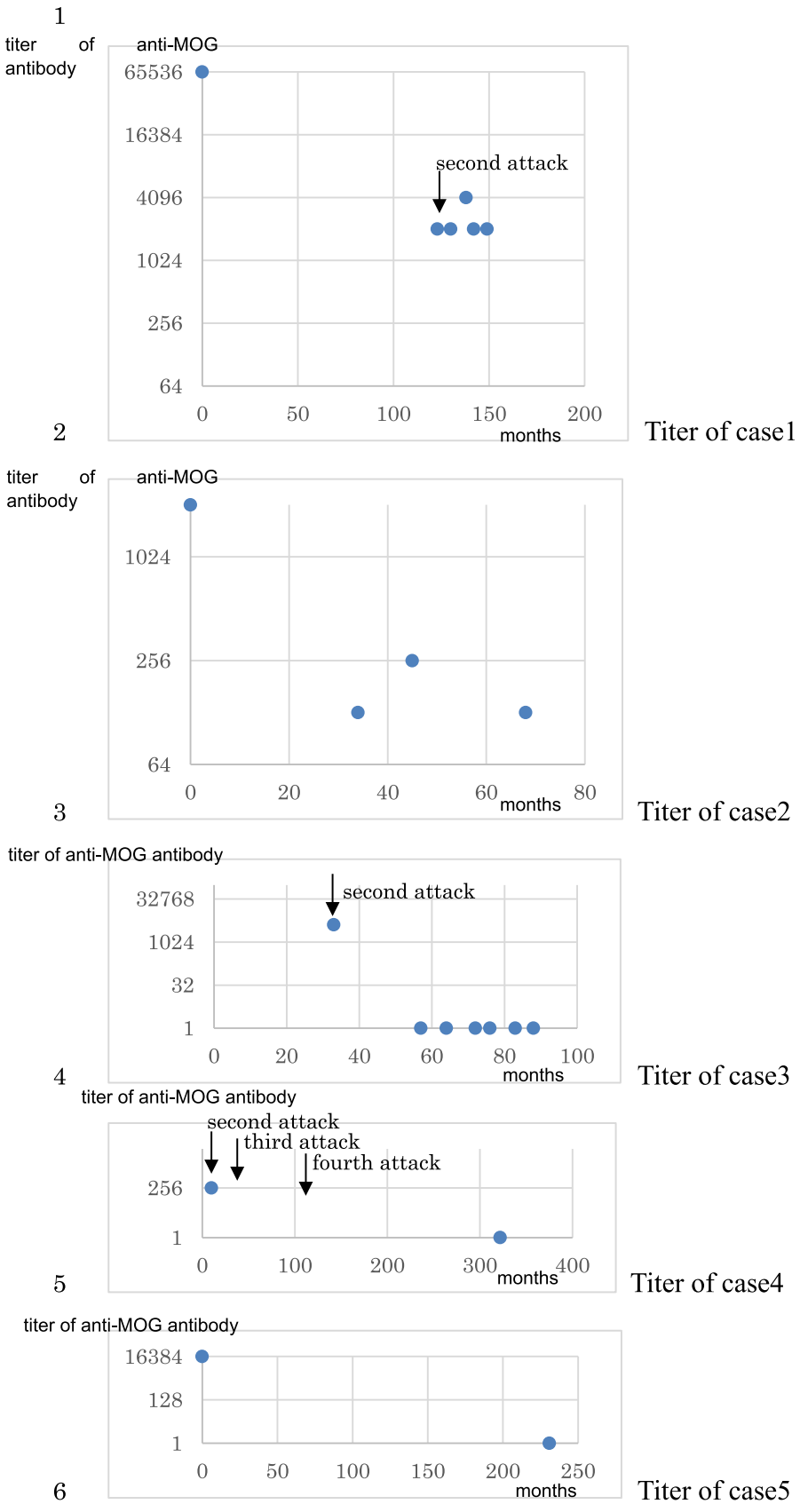

Fig. 1. Longitudinal changes of anti-MOG-antibody titer in 5 Japanese pediatric patients.

This study had two limitations. First, since the timing of sampling for anti-MOG antibody was not standardized, changes in antibody titers over time were not evaluated. Second, the study was retrospective and had a small sample size. The subjects could achieve full recovery after acute therapy with methylprednisolone pulse therapy or IVIG. It is possible that they would need additional therapy during the long-term clinical course, such as plasma exchange in addition to methylprednisolone pulse therapy or IVIG; these were not applied in the current study. Further prospective studies with larger pediatric cohorts are required to evaluate the impact of detecting anti-MOG antibodies early in the disease course, as well as the usefulness of monitoring these antibodies to facilitate long-term treatment decisions.

In conclusion, we reported our experience with very long-term follow-up of 5 Japanese pediatric patients with anti-MOG antibody-positive disease who did not receive long-term immunosuppressive therapy. Persistent positivity to anti-MOG antibody in some patients suggests the necessity for long-term follow up despite infrequent relapse.

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