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Original article

Clinical features and long-term outcome of a group of Japanese children with inflammatory central nervous system disorders and seropositivity to myelin-oligodendrocyte glycoprotein antibodies

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Abstract

Background: Myelin-oligodendrocyte glycoprotein and aquaporin-4 have been extensively analyzed as targets for humoral immune reactions in central nervous system (CNS) demyelinating diseases, and the results indicated a possible role of these antibodies in the pathogenesis of various demyelinating diseases.

Objective: To investigate the antibody titer levels against myelin-oligodendrocyte glycoprotein and aquaporin-4 in pediatric patients with inflammatory CNS disorders, and to evaluate clinical significance to study anti-myelin-oligodendrocyte glycoprotein antibodies.

Methods: Sera at onset from patients with acute disseminated encephalomyelitis (ADEM) in 7, optic neuritis (ON) in 5, pediatric MS in 4 and neuromyelitis optica in one were tested for myelin-oligodendrocyte glycoprotein and aquaporin-4 antibodies using cell-based assays with live transfected cells. The duration of the observation periods ranged from 1 to 21 years (median, 10 years). We also described clinical course of patients with positive anti-myelin-oligodendrocyte glycoprotein antibodies.

Results: Among 17 patients diagnosed with inflammatory CNS demyelinating diseases nine (52%) were positive to anti-myelin-oligodendrocyte glycoprotein antibodies. Of note, all cases with positive anti-myelin-oligodendrocyte glycoprotein antibodies showed seronegativity against anti-aquaporin-4 antibodies and had a favorable prognosis.

Conclusions: This preliminary report showed that anti-myelin-oligodendrocyte glycoprotein antibodies testing at onset could be a useful tool predicting clinical outcome of children with ADEM, ON, and MS.

Keywords: Acute disseminated encephalomyelitis; Multiple sclerosis; Optic neuritis; Neuromyelitis optica; Myelin-oligodendrocyte glycoprotein

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1. Introduction

Inflammatory demyelinating disorders of the central nervous system include a heterogeneous group of diseases such as multiple sclerosis (MS), acute disseminated encephalomyelitis (ADEM), isolated optic neuritis (ON), and neuromyelitis optica spectrum disorders (NMOSD). In clinical practice, the differential diagnosis between ADEM, isolated ON, and a clinically isolated syndrome representing the first MS attack is often challenging.

Myelin-oligodendrocyte glycoprotein (MOG) and aquaporin-4 (AQP4) have been extensively analyzed as targets for humoral immune reactions in central nervous system (CNS) demyelinating diseases, and the results suggested a possible role of these antibodies in the pathogenesis of various demyelinating diseases [1]. Interestingly, high titers of anti-MOG antibodies, assayed by cell-based assays, have been detected in a subgroup of pediatric diseases such as ADEM, MS, ON and NMOSD in different cohorts [2]. However, no study has been conducted in an Asian pediatric cohort with inflammatory demyelinating central nervous system diseases, and the follow-up period in the previous studies was not long enough to compare the long-term prognosis with typical adult MS or AQP4 antibody-positive NMOSD. In this study, we investigated anti-MOG and anti-AQP antibodies in a group of Japanese pediatric patients with inflammatory central nervous system disorders, and the final diagnosis as well as long-term prognosis was investigated retrospectively.

2. Methods

We retrospectively analyzed stored sera from 17 consecutive patients (18 years old or younger) who had been diagnosed as having inflammatory CNS demyelinating diseases at Tohoku University Hospital from 1992 to 2007. Serum samples were obtained 4–51 days (median: 8 days) after onset and before therapy. The brain magnetic resonance imaging (MRI) was studied at the onset in all patients and spinal MRI was studied in 15 patients at onset. The other diseases with white matter lesions, such as vasculitis, viral encephalitis, and metabolic disorders were excluded based on the several blood tests and lumbar puncture as well as sequential brain MRI. The patients were finally diagnosed as ADEM, ON, MS, NMO following the International Pediatric Multiple Sclerosis Study Group criteria [3]. Anti-AQP4 and anti-MOG antibodies before therapy were assayed by cell-based assays using living HEK-293 transfected cells with human aquaporin-4 M23-isoform or full-length human MOG as previously described [4,5]. The titers were calculated semi-quantitatively using consecutive two-fold end-point dilutions. This study was approved by the Ethics Committee of Tohoku University School of Medicine.

3. Results

Nine of 17 (52%) patients diagnosed with inflammatory CNS demyelinating diseases were positive for anti-MOG antibodies, among whom male predominance was evident (7 males and 2 females). A clinical summary of patients is shown in Table 1. Two patients were treated with interferon-beta (case 9 and 14). Three of eight patients diagnosed as ADEM, three of four patients diagnosed as isolated ON, three of four patients diagnosed as pediatric MS were positive for anti-MOG antibodies, while one patient with NMO was negative for anti-MOG antibodies. These anti-MOG antibody-positive patients were all negative for anti-AQP4 antibodies. All of the nine positive patients were treated in the acute phase with methylprednisolone pulse therapy and achieved full recovery. Eight of the nine patients had been under transient suspension of follow up because they were without symptoms.

The duration of the observation periods of patients who were positive for anti-MOG antibodies ranged from 1 to 21 years (median, 10 years) and we confirmed by telephone interview that all the patients maintained a good condition without further relapses or any residual neurological symptoms.

4. Discussion

This study presented good outcome and long-term prognosis of anti-MOG antibody associated diseases, although their clinical manifestations or symptoms are various among each patient as reported in the previous study [2,6].

This study has several limitations. First, since we could not repeat the test of anti-MOG antibodies, changes in its titers over time were not evaluated. Second, the retrospective nature of this study and small sample size limited the systematic evaluation of MRI and clinical parameters as well as the frequency of anti-MOG antibodies in various pediatric inflammatory CNS demyelinating diseases. Third, the prognostic efficacy of anti-MOG antibody in pediatric MS remained to be studied by using a larger sample size with MOG-positive and -negative pediatric MS.

In conclusion, we report our experience on inflammatory CNS demyelinating diseases with anti-MOG antibodies in pediatric patients initially diagnosed as having ADEM, ON, or MS. Although the number of patients was small, the positivity to anti-MOG antibodies was associated with favorable outcome, even in cases with several relapse. This preliminary report showed that anti-MOG antibodies testing at onset could be a