

Hypercomplementemia at relapse in patients with anti-aquaporin-4 antibody

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Background: Asian patients with opticospinal multiple sclerosis (OSMS) have similar features to the relapsing-remitting form of neurmyelitis optica (NMO) in Western populations. Since anti-aquaporin-4 (AQP4) antibodies are frequently detected in both patients, it is hypothesized that anti-AQP4 antibody is a causative agent for both NMO and OSMS, and that demyelination is secondarily produced following damage to the astrocyte foot process, where AQP4 is localized. As anti-AQP4 antibodies belong mainly to the IgG1 subclass, complement-mediated injury is postulated, but not yet proven in vivo.

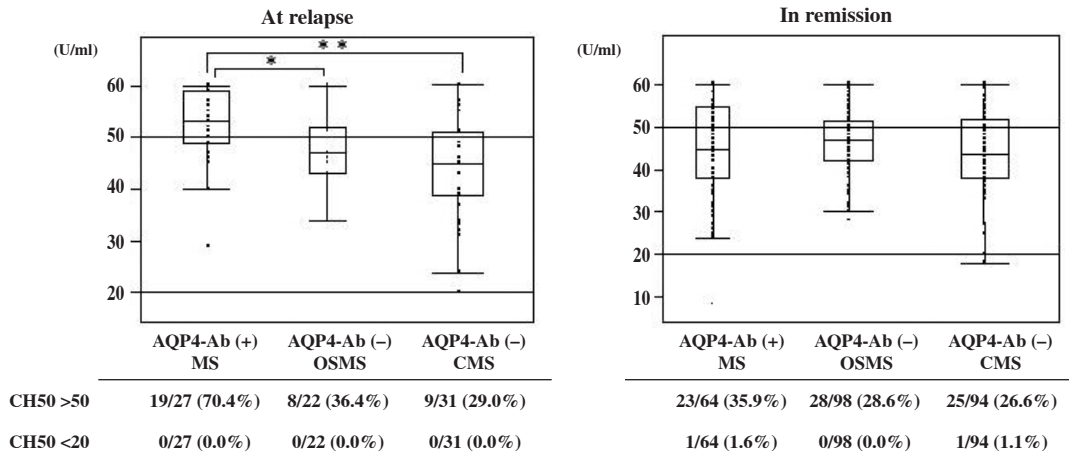
Objective: We aimed to clarify the relationships of serum complement levels with anti-AQP4 antibody status, disease phase, the extent of the CNS lesions on MRI, including longitudinally extensive spinal cord lesions and extensive white matter lesions occasionally seen in this condition, and systemic inflammatory reaction as measured by C-reactive protein (CRP) levels in multiple sclerosis (MS) patients with or without anti-AQP4 antibody.

Methods: We analyzed serum CH50, C3, C4, and CRP levels and their relation to clinical phases in 118 patients with clinically definite MS with or without anti-AQP4 antibody. In 25 patients with anti-AQP4 antibody, 19 patients (16 with OSMS and three with conventional MS) fulfilled the revised diagnostic criteria for NMO.

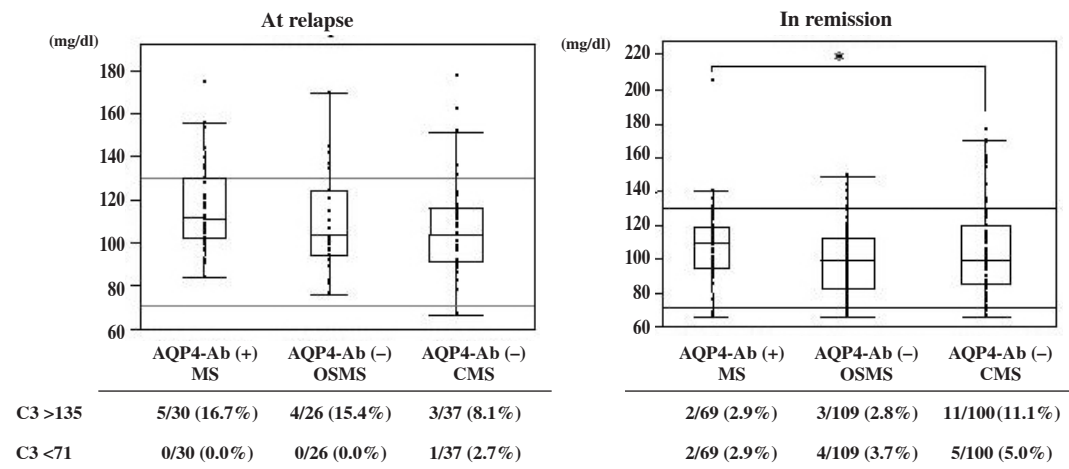
Results: Serum CH50 levels were higher in 24 patients with anti-AQP4 antibody than in 39 OSMS and 54 CMS patients without anti-AQP4 antibody at relapse ($P^{corr} < 0.05$), but not in remission (Table 1). The frequency of hypercomplementemia at relapse was also higher in anti-AQP4 antibody-positive patients than in anti-AQP4 antibody-negative CMS patients (70.4% vs. 29.0%, $P^{corr} < 0.05$). C3 and C4 levels did not differ significantly among the three groups at relapse. In patients with anti-AQP4 antibody, the coexistence of hypercomplementemia and high CRP values was more common at relapse than in the remission phase (36.0% vs. 10.5%, $P < 0.05$) (Table 2). In patients with extensive central nervous system lesions, hypercomplementemia was significantly more common in anti-AQP4 antibody-positive patients than anti-AQP4 antibody-negative ones (88.9% vs. 16.7%, $P < 0.01$) (data not shown).

Discussion: Although anti-AQP4 antibody is specifically observed in patients with relapsing NMO or OSMS, its emergence is frequently associated with systemic autoimmune diseases, such as Sjögren's syndrome and SLE. In these conditions, hypocomplementemia is especially related to acute exacerbation, reflecting complement activation and consumption in vivo. However, evidence of complement consumption was not obtained at relapse in the present study; rather, most patients had heightened CH50 activity, which is in sharp contrast to humoral immunity-mediated systemic autoimmune diseases, such as Sjögren's syndrome and SLE. Thus, most relapses in anti-AQP4 antibody-positive patients are supposed to be induced in a distinct way from those in systemic autoimmune diseases mediated by complement-fixing autoantibodies. As hypercomplementemia has been reported to occur in association with infection, malignant tumor, and vasculitis, we consider that significant increase in the number of anti-AQP4 antibody-positive patients showing both hypercomplementemia and high CRP values reflects a systemic acute inflammatory reaction at relapse.

(A) CH50



(B) C3



(C) C4

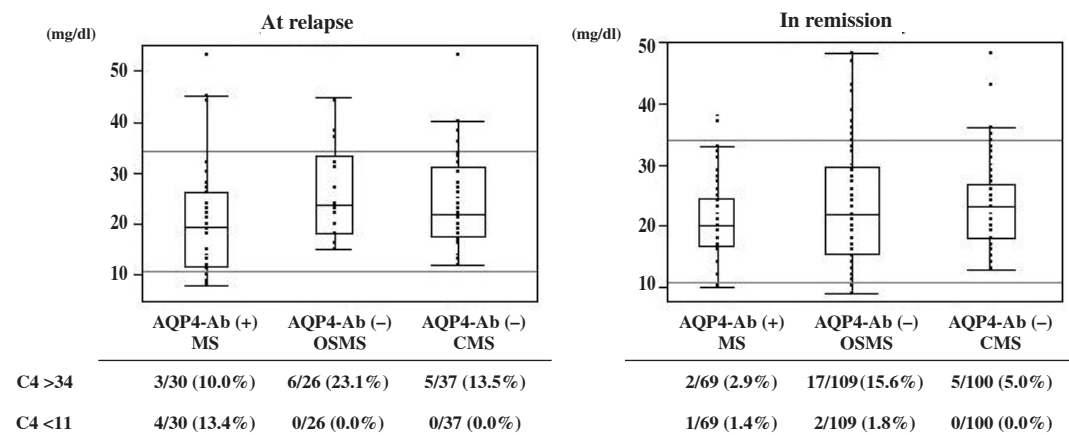
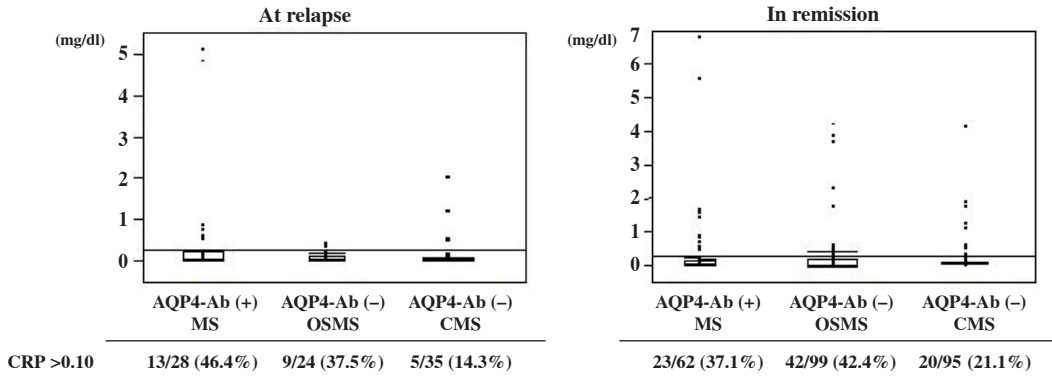


Figure 1. (A) CH50, (B) C3, and (C) C4 values in anti-AQP4 antibody-positive MS patients, anti-AQP4 antibody-negative OSMS patients, and anti-AQP4 antibody-negative CMS patients. * $P_{corr} < 0.05$, ** $P_{corr} < 0.005$.

(A) CRP



(B)

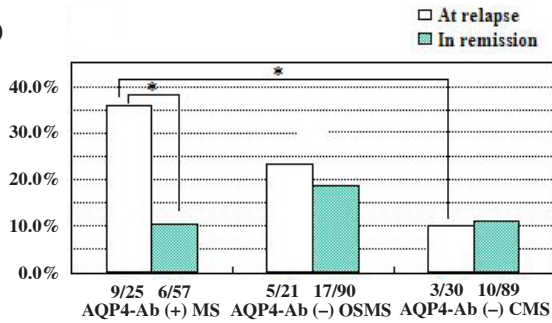


Figure 2. (A) CRP values and (B) the frequencies of patients with both hypercomplementemia and high CRP values among anti-AQP4 antibody-positive MS patients, anti-AQP4 antibody-negative OSMS patients, and anti-AQP4 antibody-negative CMS patients. * $P_{corr} < 0.05$.

References

1. Doi H, Matsushita T, Isobe N, *et al.* Hypercomplementemia at relapse in patients with anti-aquaporin-4 antibody. *Mult Scler OnlineFirst*, published on November 21, 2008 as doi: 10.1177/1352458508099139.
2. Matsuoka T, Matsushita T, Kawano Y, *et al.* Heterogeneity of aquaporin-4 autoimmunity and spinal cord lesions in multiple sclerosis in Japanese. *Brain* 2007; 130:1206-23.