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Anti-thyroid antibodies and cerebrospinal fluid findings in neuromyelitis optica spectrum disorders

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ABSTRACT

Objective: To determine the differences of thyroid diseases and ATAbs in multiple sclerosis (MS) and NMOSDs, and to assess the independent impact factors of longitudinally extensive transverse myelitis (LETM) in NMOSDs.
Results: Anti-thyroid peroxidase antibodies-positive (TPOAb(+)) and anti-thyroglobulin antibodies-positive (TGAb(+)) were most frequent in NMOSDs. LETM and lesions ≥6 vertebral segments were more frequent in TPOAb(+) NMOSDs than in TPOAb-negative (TPOAb(−)) NMOSDs. TGAb(+) NMOSDs with LETM were significantly more frequent than TGAb-negative (TGAb(−)) NMOSDs. TPOAb(+) and cerebrospinal fluid (CSF) abnormalities were independently associated with LETM.
Conclusions: Our findings demonstrate that ATAbs and thyroid diseases are significantly different in MS and NMOSD patients and CSs. TPOAb(+) and CSF abnormalities may be possible predictors of the severity of spinal cord lesions.

1. Introduction

Multiple sclerosis (MS) is a Th1-mediated autoimmune disease of the central nervous system (CNS), often alternates between phases of remission and relapse (Hafler and Weiner, 1995). Neuromyelitis optica (NMO) is a related disease, with severe inflammatory demyelination specifically affecting the optic nerves and the spinal cord (SC) (Stadelmann and Bruck, 2004). While MS involves in T lymphocytes and mononuclear macrophage reaction (Barnett et al., 2006), NMO chiefly involves in eosinophils/neutrophils and autoantibody reaction in its immunopathogenesis (Frohman and Kerr, 2007; Weinshenker, 2007). NMO is particularly common among the female gender of Japanese and Chinese populations.

Neuromyelitis optica spectrum disorders (NMOSDs) as defined by Wingerchuk et al. (2007, 2006) comprise cases of simultaneous optic neuritis (ON) and myelitis, cases of myelitis and ON, in which the two index events do not develop simultaneously but successively, and cases of limited or inaugural forms such as single or recurrent events of longitudinally extensive transverse myelitis (LETM) or recurrent ON (Weinshenker et al., 2006a, 2006b; Wingerchuk et al., 2007).

Autoimmune thyroid disease is a frequently studied disorder in MS (Munteis et al., 2007; Ramagopalan et al., 2007). Most studies have focused primarily on the increased prevalence of thyroid dysfunction and ATAbs in MS patients compared with a control population and NMO patients have increased levels of autoantibodies than MS patients (Pittock et al., 2008). Interestingly, ATAbs have been reported to be more frequently found in optic–spinal form of MS (OSMS) than in other types of MS in the Japanese population (Sakuma et al., 1999). Thyroid diseases and the relation of high-titer ATAbs with myelitis (Hamnik et al., 2008; Jarius et al., 2008) in NMO in the Asian population have also been described (Jarius et al., 2008; Nagaishi et al., 2011). However, the frequency of ATAbs and the significance of thyroid parameters, especially high-titer ATAbs with longitudinally extensive transverse myelitis (LETM) in NMOSDs is unclear.

The purpose of this study is to assess presences of ATAbs in patients with MS and NMOSDs and control subjects (CSs) and compare the clinical and magnetic resonance imaging (MRI) features in ATAbs-positive (ATAbs(+)) NMOSD and ATAbs-negative (ATAbs(−)) NMOSD subjects. Besides, we also analyzed cerebrospinal fluid (CSF) and assessed whether ATAbs and CSF abnormalities (increased CSF protein levels or white cell counts) could be independent impact factors of LETM

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[longitudinally extensive spinal cord (LESC) lesions] in Chinese NMOSD patients.

2. Methods

2.1. Study population

Enrollment for this study began in January 2008 and was completed in July 2012. Written informed consent was obtained from all patients, and the study was approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University.

All of the MS patients in this study met the McDonald diagnostic criteria for MS (Polman et al., 2005). None of the patients were on interferon-beta treatment. The diagnosis of NMO was established according to Wingerchuk's revised 2006 criteria (Wingerchuk et al., 2006). NMOSDs met the criteria proposed by Wingerchuk et al. (2007). LETM was defined as myelitis extending over 3 or more vertebral segments as detected by MRI (Weinshenker et al., 2006a; Wingerchuk et al., 2006). None of the patients were treated with corticosteroids or other immunosuppressives in the last two months prior to blood sampling.

88 persons presented with lower back pain and headache served as CSs during the same period, all of whom were also examined for the presence of non-immune or autoimmune thyroid disease. Age, age at onset of first symptoms, clinical presentation at onset, disease course and duration, and Expanded Disability Status Scale (EDSS) scores at the last visit in MS and NMOSD clinics were recorded.

2.2. ATAbs and TH analysis in serum

Serum samples were analyzed for the levels of basal thyrotropin (bTSH) and free thyroid hormones (fT3, fT4), total T3 (TT3), total T4 (TT4), anti-thyroglobulin antibodies (TGAb), and anti-thyroid peroxidase antibodies (TPOAb) by highly sensitive MAIA (magnetic antibody enzyme linking immunoassay) following the procedure of the manufacturer's instructions in all patients. The presence of associated thyroid diseases (euthyroid goiter, toxic goiter, non-thyroidal illness (NTI), chronic autoimmune thyroiditis, Hashimoto's thyroiditis and others) in patients was recorded. NTI shows pathological levels of free thyroid hormones but mostly normal bTSH and it may occur with severe chronic illness.

TPOAb and TGAb were categorized as positive or negative as per the testing laboratory protocol; titers of ≥1:60 were defined as positive for TPOAb(+) and TGAb(+). The NMOSD patients were divided into two groups based on positive presence or absence of any one of the ATAbs. The ATAbs(+) group was compared to the ATAbs(−) group to look for specific patterns of clinical and MRI features.

2.3. MRI protocol and analysis

Spinal MRI scans were performed in all patients using a GE 1.5 T MR imager scanner (General Electric, Milwaukee, WI, USA). The slice thickness of the axial scans ranged between 3 and 5 mm. Conventional MRI protocols were used in all patients: T1 with and without gadolinium enhancement (400/15.5 ms, TR/TE) and T2 (2500–3500/100 ms, TR/TE) in spinal cord MRI and T2 (4600–4640/97.8–102 ms, TR/TE) and fluid attenuated inversion recovery (FLAIR) (8800/120 ms, TR/TE) in brain MRI.

All MRI scans were performed prior to corticosteroid treatment and after serum sampling. No patients were receiving interferon-beta or immunosuppressants at the time of MRI scanning. All MRI scans were analyzed by one experienced neuroradiologist who was blinded to the diagnostic categorization and the patients' clinical features. If more than one lesion was present in the same MRI, the longest lesion was counted; the number of the longest lesion segments was considered as SC lesions. The cumulative length of all lesion segments present in the same SC MRI was considered as the total lesion load (see Table 4). The patients were further divided into 2 groups with SC lesions ≥3 and <3.

2.4. Antibodies to aquaporin-4 (AQP4-Ab) testing and CSF analysis

The serum samples were detected by AQP4-Ab transfected cells from a commercial sampling kit (Euroimmun Company, Germany) according to the manufacturer's instruction. Sera were scored negative or positive by one assessor, who was also blinded to the clinical diagnosis.

After obtaining informed consent, CSF was collected from patients prior to treatment with methylprednisolone. The CSF sample was used for routine analysis.

2.5. Statistics analyses

Continuous data were compared by Student's t-test or the Mann–Whitney U test. A chi-square test or Fisher's exact test was used to evaluate the nominal variables. Mean values were given with standard deviation. Age, age of onset, disease duration, number of relapse, thyroid disease, CSF analysis, AQP4-Ab and TPOAb or TGAb were entered into logistic regression analyses. p values <0.05 were considered statistically significant. Statistical analysis was performed by SPSS version 16.0 (IBM, Armonk, NY).

3. Results

3.1. Demographics of MS and NMOSD patients

A total of 30 patients fulfilled the inclusion criteria for MS and 50 patients met the NMOSD criteria. Table 1 shows the clinical characteristics of the study population. 40 patients with NMOSDs (80%) were AQP4-Ab positive. The 30 patients with MS (female/male: 18/12) had disease onset at the age of 31.8 (11.0) years (range: 10–55), mean disease duration of 24.3 (33.0) months (range: 0.3–156.0), median number of relapse of 3 (range: 1–10), and a mean EDSS score of 3.7 (2.2) (range: 1.0–9.5). The 50 patients with NMOSDs (female/male 45/5) had disease onset at the mean age of 36.3 (12.4) years (range: 15–64), mean disease duration of 35.5 (49.2) months (range: 12.0–238.0), median number of relapse of 3 (range: 1–19), and a mean EDSS score of 5.0 (2.2) (range: 1.5–9.0). The 88 CSs (female/male: 60/28) had mean age of 36.3 (11.4) years (range: 18–57). These CSs matched the MS group for age and sex and matched the NMOSD group for age.

3.2. Frequency and distribution of thyroid disease and ATAbs between MS and NMOSDs

The distribution of thyroid diseases and the subtypes of ATAbs in patients with MS and NMOSDs and CSs are shown in Table 2. Thyroid diseases showed a significantly higher prevalence in NMOSD patients than in MS patients (30.0% vs. 6.7%, $p = 0.014$). TPOAb(+) were detected in 4/88 (4.5%) CSs, compared to 7/30 (23.3%) MS ($p = 0.007$) and 20/50 (40.0%) NMOSD ($p < 0.001$) patients. TGAb(+) were detected in 5.7% of the CS population, compared to 16.7% in the MS group ($p = 0.134$) and 30.0% in the NMOSD group ($p < 0.001$).

3.3. Clinical correlation between ATAbs(+) and ATAbs(−) in NMOSDs

The gender ratio and age were similar between TPOAb(+) and TPOAb(−) patients. No difference was found in disease duration, number of relapse, EDSS score, clinical presentation at onset, and CSF abnormalities between them. However, NMOSD patients with TPOAb(+) had younger age of onset (31.2 vs. 39.0 years, $p = 0.031$). Compared to the TPOAb(−) group, the group with TPOAb(+) had a higher percentage of patients with thyroid diseases (50.0% vs. 16.2%, $p = 0.012$). The TPOAb(+) group had a higher percentage of positive AQP4-Ab (95.0% vs. 66.7%, $p = 0.043$) (Table 3).