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Differentiation of neuromyelitis optica spectrum disorders from ultra-longitudinally extensive transverse myelitis in a cohort of Chinese patients

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ABSTRACT

This study aimed to differentiate neuromyelitis optica spectrum disorders (NMOSD) from other causes in cases of ultra-longitudinally extensive transverse myelitis (uLETM). We retrospectively analyzed thirty-three Chinese patients with uLETM hospitalized in the China–Japan Friendship Hospital. The patients were divided into NMOSD (n = 21) and non-NMOSD (n = 12) groups. The NMOSD group exhibited significantly more comorbidity compared with the non-NMOSD group; moreover, the NMOSD group uniquely exhibited intractable vomiting and hiccups (IVH). The prevalence rates of cervicothoracic, area postrema (AP), and other circumventricular organ (CVO) lesions were significantly increased in the NMOSD group compared with the non-NMOSD group. Moreover, uLETM was strongly associated with NMOSD. These novel findings indicate that CVO lesions, including AP, and particularly when combined with clinical IVH, may represent a useful discriminator to differentiate NMOSD.

1. Introduction

Longitudinally extensive transverse myelitis (LETM) is a relatively rare spinal cord syndrome, which was included as a critical supportive criterion for neuromyelitis optica (NMO) by Wingerchuk (Wingerchuk et al., 2006). LETM was also characterized as a main type of the NMO spectrum disorders (NMOSD) with seropositive aquaporin 4 antibody (AQP4-IgG) in the following year (Wingerchuk et al., 2007). The majority of LETM studies to date have focused on the lower limits of the spinal cord segments involved, using a cut-off point of three vertebrae to distinguish NMOSD from multiple sclerosis (MS) (Wingerchuk et al., 2006; Wingerchuk et al., 2007; Kitley et al., 2012; Kitley et al., 2013). However, to the best of our knowledge, few case reports have specifically discussed longer spinal cord lesions, and these cases are almost exclusively cases of LETM secondary to systemic lupus erythematosus and paraneoplastic myelopathy (Tellez-Zenteno et al., 2001; Flanagan et al., 2011).

We have previously reported four cases of transverse myelitis with whole spinal cord injury; in these cases, one patient died and two patients had severe residual disability (Zhang et al., 2011). Thus, we termed the more severe form of transverse myelitis that we observed, with lesions in the spinal cord that extend over ten or more vertebrae, as ultra-LETM (uLETM) (Zhang et al., 2011). Although the four previously reported patients eventually developed NMOSD (Zhang et al., 2011), uLETM was not caused by NMOSD in all patients (Jiao et al., 2014; Wang and Li, 2015), which may obscure the diagnosis, particularly for patients who have limited forms of NMOSD, such as monophasic LETM, or the less common optic neuritis. The identification of the underlying etiology at the initial visit is critical to initiate appropriate therapy and optimize outcomes. The aim of this study was to determine the etiologic

Abbreviations: LETM, longitudinally extensive transverse myelitis; NMO, neuromyelitis optica; NMOSD, NMO spectrum disorders; AQP4-IgG, aquaporin 4 antibody; MS, multiple sclerosis; uLETM, ultra-LETM; IVH, intractable vomiting and hiccups; CSF, cerebrospinal fluid; CVO, circumventricular organs; ADEM, acute disseminated encephalomyelitis; SDAVF, spinal dural arteriovenous fistula; PM, paraneoplastic myelopathy; iLETM, isolated LETM; AP, area postrema; EDSS, expanded disability status scale; IST, immunosuppressive treatments; FU, follow up; LON, left optic neuritis; BON, bilateral optic neuritis; TM, transverse myelitis; SS, Sjogren's syndrome; HT, Hashimoto's thyroiditis; IVMP, intravenous methylprednisolone; IVIg, intravenous immunoglobin; TPE, therapeutic plasma exchange; AZA, azathioprine; MMF, Mycophenolate Mofetil; CTX, intravenous cyclophosphamide; CS, corticosteroids; IFN-β, interferon-β; N/A, not available.

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distribution of uLETM patients and to identify discriminators that differentiate NMOSD from other causes via a retrospective analysis of a series of Chinese uLETM patients. To the best of our knowledge, this is the first study to distinguish NMOSD from uLETM in a Chinese cohort.

2. Methods

2.1. Patients

Thirty-three (22 women and 11 men) Chinese patients with uLETM, who were hospitalized at the China–Japan Friendship Hospital (Beijing, China) between January 2009 and April 2015, were consecutively enrolled in our study. Patients were divided into two groups based on the presence or absence of NMOSD (e.g., the NMOSD and non-NMOSD groups, respectively). The following parameters were retrospectively analyzed and compared between the two groups: demographic data (age and gender), etiologic classification, clinical features (e.g., onset form, intractable vomiting and hiccups (IVH), comorbidity, and AQP4-IgG status), and imaging features (e.g., spinal cord segments involved, distribution and extent of spinal and brain lesions, and contrast lesions on MR images). The onset severity of uLETM in the NMOSD and non-NMOSD patients was assessed using the Expanded Disability Status Scale (EDSS, range 0–10). The study was approved by the Institutional Review Board of the China-Japan Friendship Hospital, and informed consent was waived by the committee.

2.2. Inclusion criteria

Patients with clinical signs and symptoms of myelopathy, with at least one concurrent lesion in the spinal cord that extended over ten or more vertebrae on T2-weighted MRI scans, were included. The 2015 International Consensus Diagnostic Criteria were used for NMOSD with or without AQP4-IgG (Wingerchuk et al., 2015).

2.3. Laboratory data

AQP4-IgG was analyzed using a cell-based assay (AQP4-IgG test kit; EUROIMMUN (China) Co., Beijing, China) by an independent medical inspection agency. Serum specimens were collected during the acute phase or clinical relapse in 27 cases, including 20 cases of NMOSD. All AQP4-IgG samples were collected before the attack or maintenance treatments, with the exception of two patients in the NMOSD group, who received interferon-β and low-dose corticosteroid therapy, respectively. Anti-myelin oligodendrocyte glycoprotein antibodies were not recorded for the cases who exhibited seronegative AQP4-IgG. The cerebrospinal fluid (CSF) cell count, glucose concentration, and protein levels were recorded. Serum and CSF antibodies against herpes simplex virus, adenovirus, cytomegalovirus, varicella-zoster virus, Epstein–Barr virus, and enterovirus were considered, when necessary. The serum of all patients with suspected sarcoidosis was tested for angiotensin-converting enzyme. We recorded well-recognized serum antibodies, as well as CSF onconeural antibodies [e.g., anti-Hu (ANNA-1), anti-Yo (PCA-1), anti-Ri (ANNA-2), anti-CV2 (CRMP5), anti-amphiphysin, and anti-Ta/Ma2] in cases of suspected paraneoplastic myelopathy.

2.4. Imaging data

Spinal cord MRI was performed on a SignaHDX-3.0T (General Electric Co., Fairfield, CT, USA) or GYROSCAN-1.5T (PHILIPS Co., Amsterdam, Holland) nuclear magnetic resonance scanner. MRI scanning covered the cervical, thoracic, and lumbar spine. T1-weighted sequences with and without gadolinium were obtained. T2-weighted sequences were used to obtain sagittal and axial images. We delineated the affected area as transverse sections of complete and partial lesions, the spinal cord segments involved (number of vertebral segments), and their location in the sagittal image (cervicothoracic, thoracic or whole segments). We also recorded the circumventricular organ (CVO) lesions and gadolinium contrast lesions, when available.

2.5. Statistical analysis

All statistical analyses were performed using SPSS 22.0 software (IBM Corp., Armonk, NY, USA). Statistical significance was set at $p < 0.05$. The median age of uLETM onset, nadir EDSS for uLETM, and involved segments (vertebrae number) were analyzed using Mann–Whitney U tests. Differences in the sex ratio and other clinical and imaging parameters between the NMOSD and non-NMOSD groups were analyzed using Fisher's exact tests.

3. Results

3.1. Etiological distribution across uLETM patients

In our cohort, 21 of 33 cases fulfilled the diagnosis of NMOSD. The detailed clinical characteristics of the NMOSD patients are summarized in Table 1.

One AQP4-IgG seronegative case exhibited concurrent multiple brain lesions after brain surgery. The patient was diagnosed with acute disseminated encephalomyelitis (ADEM), which was attributed to a monophasic course during the previous four-year follow-up. Three middle-aged men who presented with chronic progressive spastic paraplegia with mild sensory and sphincter disorders were diagnosed with spinal dural arteriovenous fistula (SDAVF); two patients received interventional embolization therapy and recovered gradually, whereas another patient was lost to follow-up. One 62-year-old woman was diagnosed with paraneoplastic myelopathy (PM) and manifested subacute myelopathy with breast cancer, which was identified before the onset of PM; the patient's ability to walk progressed slowly over three years of follow-up. One 32-year-old woman with leukemia-related myelopathy secondary to acute myelocytic leukemia exhibited an acute onset paraplegia and serious sphincter disorders; despite the timely application of leukemia chemotherapy, the patient died within six months. One 18-year-old woman with infectious mononucleosis manifested with high fever, an enlarged liver, spleen, and lymph nodes, and a positive screen for EB virus antibodies in the serum and CSF; she obtained full recovery within one year after receiving antiviral therapy combined with five sessions of therapeutic plasma exchange (TPE). One 69-year-old woman was diagnosed with Arnold-Chiari malformation associated with syringomyelia. The manifestations of the remaining four uLETM patients could not be classified as belonging to any of these diseases and were referred to as isolated LETM (iLETM); these four patients received attack immunotherapies (i.e., intravenous methylprednisolone and/or TPE) and remained relapse-free for at least three years.

3.2. Comparison of clinical features between NMOSD and non-NMOSD patients

The comparison of clinical features in the NMOSD and non-NMOSD groups is summarized in Table 2. In the NMOSD group, there were predominantly female patients (17/21 [81.7%]) who exhibited an acute or subacute onset (20/21[95.2%]) compared with the non-NMOSD patients (5/12 [41.7%] and 7/12 [58.3%], respectively, $p < 0.05$). Nine patients (42.9%) exhibited comorbid systemic diseases, which significantly increased compared with the non-NMOSD patients (1 [8.3%]; $p < 0.05$). Nine patients (42.9%) exhibited IVH, and 14/20 patients (70.0%) exhibited seropositive AQP4-IgG. The median age of uLETM onset was not significantly different between the NMOSD group (33.0 [23.0] years) and the non-NMOSD group (47.0 [20.5] years). The median nadir EDSS for uLETM in the NMOSD group (7.0 [3.5]) was similar to the non-NMOSD group (5.0 [3.7]). Furthermore, there were no