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Prognostic value of oligoclonal IgG bands in Japanese clinically isolated syndrome converting to clinically definite multiple sclerosis

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ABSTRACT

We evaluated the impact of brain MRI findings and oligoclonal IgG bands (OCBs) on conversion to clinically definite multiple sclerosis (CDMS) in 26 Japanese patients with clinically isolated syndrome (CIS). 19.2% had OCBs positivity and 3.8% had fulfillment of Barkhof criteria at baseline. 60.0% of CIS patients with positive OCBs and 9.5% of those with negative OCBs developed CDMS during 60.6 months. Japanese CIS patients with positive OCBs have an equivalent risk of developing CDMS. A hypothesis that Japanese CIS patients may have substantially less OCBs positivity, MRI lesions, and conversion ratio than Caucasians, should be further tested.

1. Introduction

Clinically isolated syndrome (CIS) is the first demyelinating event in the central nervous system and heralds clinically definite multiple sclerosis (CDMS) (Miller et al., 2005; Miller et al., 2012). In previous studies the ratio of the conversion from CIS to multiple sclerosis (MS) widely ranges from 5.6 to 68%, at least partially because of the diversity of follow-up period and difference in diagnostic criteria of MS among studies (Swanton et al., 2010; Brex et al., 2002). Therefore the natural clinical course of conversion to CDMS has been not fully understood.

Presence of multiple brain lesions on MRI at the onset of CIS has been associated with high risk to convert MS (Miller et al., 2012; Fisniku et al., 2008; Tintoré et al., 2008; Kuhle et al., 2015). Positive oligoclonal IgG bands (OCBs) is another predictive factor for the conversion in European patients that doubles the risk of the second attack, independently of MRI (Tintoré et al., 2008; Kuhle et al., 2015). However, considering that the incidence and the clinical presentation widely variable by race/ethnicity in a similar pattern to MS (Langer-Gould et al., 2014), and that CIS patients in Japan tend to show less brain lesions than those in western countries (Tanaka et al., 2012), it is worth analyzing whether these predictive factors are also applicable to Asian patients.

Here we evaluated the impact of brain MRI lesions and positive OCBs in the cerebrospinal fluid at the onset on the conversion in Japanese patients. For comparison we also investigated ratio of CDMS conversion using a systematic literature review. Part of this manuscript was presented in the 66th Annual Meeting of the American Academy of Neurology, 2014, in an abstract form.

2. Materials and methods

2.1. Patients

In this prospective study, we consecutively enrolled all patients who visited the Neurology Clinic in Utano National Hospital with the first demyelinating event between February 2006 and May 2014, and who fulfilled with the inclusion criteria of 1) first event of symptoms suggestive of acute demyelination of the central nervous system, 2) adequate laboratory and magnetic resonance imaging (MRI) examinations that exclude other neurological diseases, and 3) cerebrospinal fluid (CSF) analyses included OCBs and serum anti-aquaporin 4 (anti-AQP4) antibodies. We excluded patients with neuromyelitis optica-related

Abbreviations: CDMS, clinically definite multiple sclerosis; CIS, clinically isolated syndrome; HR, hazard ratio; MS, multiple sclerosis; OCBs, oligoclonal IgG bands; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; AQP4, aquaporin 4; NMOrd, neuromyelitis optica-related disorder.

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disorder (NMOrd), i.e., who demonstrated anti-AQP4 antibodies and/or centrally located longitudinally extensive spinal cord lesions on spinal cord MRI. CDMS was diagnosed with the second clinical attack caused by different lesion (Poser et al., 1983).

All clinical assessments including MRI, CSF, and serum analyses were performed as part of the thorough diagnostic evaluation. This study was conducted according to policy of the Specified Disease Treatment Research Program, based on the opinions of the Specified Disease Conference, an advisory body for the Health Service Bureau of the Ministry of Health, Labour and Welfare of Japan.

2.2. Cerebrospinal fluid and serum analysis

CSF and serum samples were collected at Utano National Hospital. The presence of OCBs was examined using isoelectric focusing method with immunoblotting of matched serum and CSF sample pairs in a commercial clinical laboratory (BML, Tokyo). Anti-AQP4 antibodies were examined using a cell-based assay (Tanaka et al., 2007).

2.3. Brain MRI

Basically, brain MRI scans were taken at a matrix size of 192 × 220, with a gap of 10% between each 5.0 mm thick slice parallel to the foramen of Monro–posterior commissure reference line using the Siemens MAGNETOM Symphony Syngo 1.5-T MRI system (Siemens Japan K.K., Tokyo). T1-weighted images (TR 480–556 ms, TE 10 or 11 ms) with gadolinium enhancement (meglumine gadopentetate or gadodiamide hydrate) and T2-weighted images (TR 2980–3830 ms, TE 93–131 ms) were evaluated for fulfillment of number of Barkhof criteria (Barkhof et al., 1997) by a single examiner (M.K.) blinded to patients' clinical data for the purpose of the current study, independent from therapeutic decision making.

2.4. Inclusion criteria for a literature review and search strategy

In order to compare our data with the literature, we investigated ratio of CDMS conversion using a systematic literature review (Fig. 1). We included original articles which demonstrate (a) ratio and/or number of patients of conversion from CIS to CDMS and follow up length, and in which (b) CDMS was diagnosed with the second clinical attack caused by different lesion, or according to Poser's criteria when further clinical information could not be obtained (Poser et al., 1983). Data of the conversion ratio were obtained by a systematic literature review. PubMed search using the terms 'isolated syndromes' and 'multiple sclerosis' yielded 983 articles, and 'multiple sclerosis' and 'follow' yielded 4057 articles (accessed 5th Mar 2014). Then, hand search of the resulting abstracts followed by referring to the whole manuscript, 23 articles fulfilled with the both inclusion criteria (Swanton et al., 2010; Sormani et al., 2008; D'Alessandro et al., 2013; Zipoli et al., 2009; Alroughani et al., 2012; Tintoré et al., 2001; Villar et al., 2011; Rocca et al., 2008; Tintoré et al., 2008; Ruet et al., 2011; Tintoré et al., 2006; Morrissey et al., 1993; Rojas et al., 2010; Villar et al., 2008; Masjuan et al., 2006; Patrucco et al., 2012; Chard et al., 2011; Tintore et al., 2010; Minneboo et al., 2004; Morrow et al., 2010; Brex et al., 2002; Dalton et al., 2012; Fisniku et al., 2008). When only number of the suitable patients or ratio in subgroups was provided, we calculated the ratio of CDMS conversion based on the clinical information provided.

2.5. Statistics and model analyses

Mann-Whitney *U* test was used to compare differences between groups, and Fisher's exact test was used in the analysis of contingency tables. A p value less than 0.05 was regarded as statistically significant. To obtain the most suitable model to represent the empirical data from literature review, we performed parametric curve-fitting analysis to correlate ratio of conversion to CDMS against time. All analyses were performed using SPSS 16.0J (IBM Japan, Tokyo).

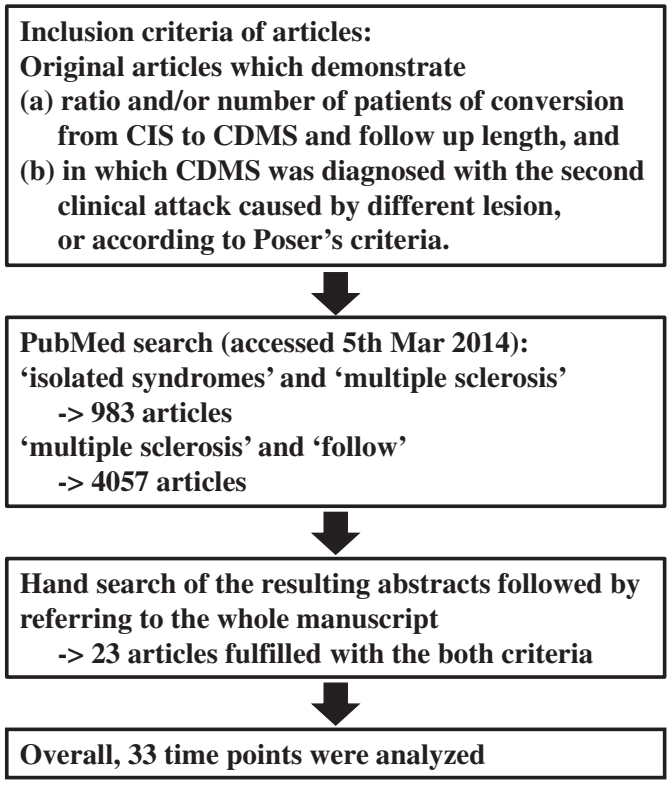

Fig. 1. Flow chart showing study selection procedure.