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Whole brain and grey matter volume of Japanese patients with multiple sclerosis

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ABSTRACT

We evaluated the brain volume and rate of atrophy in 85 Japanese patients with multiple sclerosis (MS). The mean brain volume was smaller and the rate of atrophy appeared to be more rapid in MS patients than in normal subjects. The brain atrophy seemed to exist from the early stage of MS and was prominent in the grey matter. Patients with progressive MS showed severer atrophy. We show the existence of pathological brain atrophy in Japanese MS patients for the first time, although the rate of atrophy may be much slower than in Caucasian patients.

1. Introduction

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS) with multiple lesions in the brain, optic nerves, and spinal cord (Compston and Coles, 2008). Oligodendrocytes, which compose the myelin sheath in the CNS, are mainly damaged (Lucchinetti et al., 2000). Although relapsing and remitting inflammation based on autoimmunity has long been considered the main pathomechanism in MS, the continuous degenerative process, accompanied by brain atrophy, has also received attention (Ge et al., 2000; Fox et al., 2000). In the past, the treatment aim in MS was mainly to reduce the occurrence and duration of relapses. Subsequently, a disease status of no disease activity, referred to as "no-evidence of disease activity" (NEDA), defined as the complete absence of clinical relapses, with no increase of clinical disability and no newly active lesion on brain MRI, was introduced as the optimal treatment outcome in MS (Giovannoni et al., 2015; Banwell et al., 2013; Rotstein et al., 2015; Stangel et al., 2015). More recently, a revised version of NEDA, known as NEDA4, has been introduced, in which a rate of brain volume loss below 0.4% per year has been added to the criteria (Kappos et al., 2016). Although some conventional disease-modifying drugs (DMD) may suppress the degenerative process, treatments that stop the degenerative process are vigorously sought (Branger et al., 2016).

As the importance of the degenerative process in MS has gradually come to be recognized, more volumetric technologies using MRI imaging (e.g. SIENAX, NeuroQuant, and MSmetrix) have been developed (Ge, 2006; Jain et al., 2015; Wang et al., 2016; Lysandropoulos et al., 2016). Volumetric data in Caucasian MS patients suggested that brain atrophy would be severer and faster in MS patients than in the normal population (Fisher et al., 2008; Fox et al., 2000; Ge et al., 2000; Kalkers et al., 2002; Sanfilipo et al., 2005). In a small number of Chinese MS patients, the brain volume was also shown to be smaller than in controls (Lin et al., 2013). However, at present, there are no data available about brain volume changes in a large number of Japanese MS patients.

In this study, we cross-sectionally assessed the brain volume and fluid-attenuated inversion recovery (FLAIR) lesion volume in Japanese MS patients, together with other clinical information. With these data, we evaluated the brain volume atrophy in Japanese MS patients compared with those in the normal population and searched for factors contributing to the brain atrophy in MS patients. We also compared the rate of brain atrophy in Japanese patients with that in Caucasian patients reported in previous studies.

2. Material and methods

2.1. Patient enrollment

Consecutive MS patients who were treated in the outpatient clinic of Tohoku University Hospital as of 2016 and agreed to participate in this

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volumetric study were enrolled for this study. The diagnosis of MS was done based on the revised McDonald criteria (Polman et al., 2011; McDonald et al., 2001). Patients with serum anti-aquaporin-4 (AQP4) autoantibody or serum anti-myelin oligodendrocyte glycoprotein (MOG) autoantibody, both of which were measured by a cell-based assay in Tohoku University before the enrollment, were excluded without exception from this study (Sato et al., 2014). MS patients with other brain diseases such as cerebrovascular disease and progressive multifocal leukoencephalopathy (PML) were also excluded from this study. Finally, a total of 85 MS patients were enrolled; 84 were Japanese and 1 was Armenian. Their cross-sectional clinical data were comprehensively studied.

For the comparison, brain volume data from a total of 1282 people (762 female and 520 male) of a normal Western world population, comprised of multiple ethnicities, collected by Icometrix (Leuven, Belgium), were used as a control.

2.2. The clinical information collected

The following clinical information was comprehensively collected from 85 patients in 2016: sex, present age, onset age, disease duration, expanded disability status scale (EDSS) and MS severity score (MSSS), total number of relapses in the past, and the details of DMD usage (Kurtzke, 1983; Roxburgh et al., 2005). All patients were classified into the following three MS subtypes: relapsing-remitting MS (RRMS), secondary-progressive MS (SPMS), and primary-progressive MS (PPMS).

Among the enrolled patients, 36 underwent lumbar puncture at the onset, and the following laboratory data of the cerebrospinal fluid were collected: positivity of oligoclonal bands (OCB), quotient of albumin (Q_{Alb}), quotient of immunoglobulin G (Q_{IgG}), and IgG-index.

2.3. Volumetry of the brain and lesion volume

Three-dimensional FLAIR and three-dimensional T1-weighted image sequences were obtained by 3-Tesla Philips Ingenia CX MRI system (Royal Philips Electronics, Netherland). The imaging data of each patient were analyzed using MSmetrix program by uploading the DICOM data to a website of Icometrix (http://icometrix.com). The MSmetrix method takes into account both the T1-weighted and the FLAIR images in an iterative process to obtain tissue (white matter, grey matter, cerebrospinal fluid) and lesion segmentations. For volumetric computation, a lesion-filled T1-weighted image was created by replacing lesion voxels with values matching the white matter tissue intensities on the bias field corrected T1-weighted image. Thus, in the final lesion-filled T1-weighted image segmentation, lesions are included in the white matter segmentation and contribute to the whole brain volume without the risk of overestimating the grey matter volume. The analysis report (Fig. 1) included the whole brain volume, grey matter volume, and FLAIR-lesion volume, together with the age-matched normal range (Lysandropoulos et al., 2016; Jain et al., 2015).

2.4. Comparison of age-adjusted brain volume

Scatter plots with volumetric data and the present age were depicted both in MS patients and in controls. Plots from the two groups were superimposed on the same chart to graphically compare the age-adjusted distribution.

2.5. Statistical analyses and software

Both in MS patients and controls, volumetric data were compared between males and females to determine possible sex-based differences with Student's *t*-test.

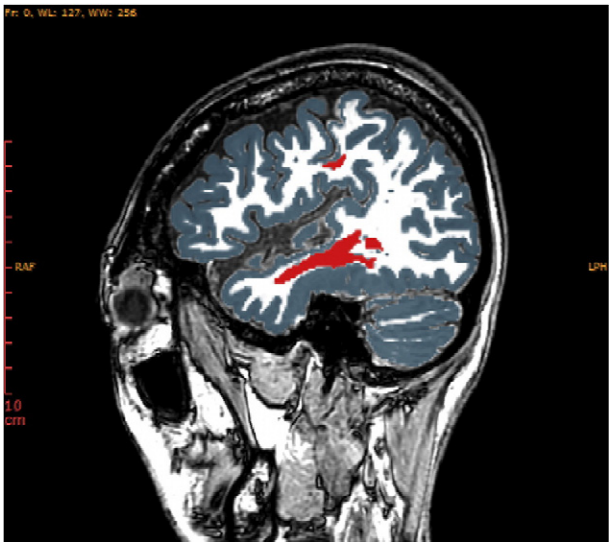

Fig. 1. An example of an MSmetrix report showing the grey matter volume and FLAIR lesion volume. This is a picture showing a part of the MS metrix report, which separately measures the grey matter volume (deep blue) and FLAIR lesion volume (red).

Correlation coefficients between each pair of variables were comprehensively evaluated. Correlation coefficients were all measured as Spearman's rank correlation coefficients, followed by the test of no correlation. Because tests of no correlation with multiple pairs were simultaneously done, p-values < 0.001 were regarded as significant.

For the statistical comparisons between MS and controls, we used sex- and age-matched controls ($n = 85$; 23 males and 62 females) to compare with the rate and distribution in the MS patients. Statistical comparisons of the data between MS and age-matched control groups ($n = 85$ for both) were done with Student's *t*-test, Mann-Whitney's *U* test, or chi-squared test, based on the distribution pattern and type of each variable.

Because comparisons in multiple variables were simultaneously done, p-values < 0.001 were regarded as significant.

Comparison of the annual rate of brain atrophy between MS ($n = 85$) and controls ($n = 1282$) was done with analysis of covariate (ANCOVA) using the present age as a covariate.

Statistical analyses were conducted using SPSS Statistics Base 22 software (IBM, Armonk, NY, USA) and MATLAB R2015a (MathWorks, Natick, MA, USA).

2.6. Institutional Review Board

The Institutional Review Board (IRB) of Tohoku University Hospital reviewed and approved the study protocol. All enrolled patients were explained the purpose of this study and gave signed, informed consent before their enrollment.

3. Results

3.1. Clinical information of the enrolled patients

Among the 85 enrolled patients, 61 were female (71.8%) and 24 were male (28.2%). Present ages were 39.1 ± 10.1 years old; onset ages were 28.3 ± 8.1 years old. Median and range of EDSS in 2016 were 2.0 (0.0–9.0); the mean ± SD of MSSS in 2016 was 3.0 ± 2.6. Total numbers of relapse in the past as of 2016 were 4.4 ± 3.6. Their MS subtypes, based on revised criteria proposed by Lublin et al. in 2014, were as follow: 72 were RRMS, 11 were SPMS, and 2 were