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Brain volume in early MS patients with and without IgG oligoclonal bands in CSF

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ABSTRACT

Background: Oligoclonal bands of IgG (OB) are proposed as an early prognostic factor of the disease. Growing attention is directed towards brain volume evaluation as a possible marker of the severity of MS. Previous studies found that MS patients lacking OB have less brain atrophy.
Aim: to evaluate a possible relationship between OB and cerebral volume in a cohort of early MS patients.
Methods: Inclusion criteria were: diagnosis of relapsing-remitting MS; CSF analysis and MRI acquired simultaneously and within 12 months from clinical onset. A total of 15 healthy controls underwent MRI.
Results: In 20 MS patients, CSF analysis did not show OB synthesis (OB negative group). A control group of 25 MS patients in whom OB was detected was also randomly recruited (OB positive group). T test showed a significant difference in NWV between the OB positive and OB negative groups (P value = 0.01), and between the OB positive group and the healthy controls (P value = 0.001). No differences were detected between OB negative group and healthy controls.

Multivariable linear regression showed a relationship between NWV and OB synthesis (P value = 0.02) controlling for age, gender, and EDSS.
Conclusions: Our preliminary results suggest that OB positive patients show more atrophy of white matter since early phases of the disease, supporting the role of CSF analysis as a prognostic factor in MS.

1. Introduction

Multiple sclerosis (MS) is a chronic disease of the central nervous system. Although the aetiology remains unknown, it is generally assumed that genetic susceptibility combined with exposure to environmental factors is required for its development (Cocco et al., 2012).

Both inflammation and neuro-degeneration are involved from the early stages (Haider et al., 2016). Although MS diagnosis is defined based on clinical features, radiological and biological markers are generally used in clinical practice to confirm diagnosis and exclude MS mimicking pathologies (Brownlee et al., 2017). These biomarkers and features have also been evaluated as possible prognostic factors (Confavreux and Vukusic, 2014). MRI is certainly the principal paraclinical tool in the diagnosis and monitoring of MS, and the most comprehensively evaluated prognostic factor (Wattjes et al., 2015).

Among MRI outcome measures, attention is increasingly directed at the volume of whole brain, white, and grey matter. Indeed, brain volume analysis has been proposed as a possible expression of a diffuse pathology that is strictly correlated to other clinical measures (De Stefano et al., 2014). Some studies have highlighted a correlation between cerebral atrophy, relapses, disability, and long-term progression (Rudick et al., 2000; Di Filippo et al., 2010). An impact of MS on cerebral volumes is detected from the early stages of the disease (Vidal-Jordana et al., 2016).

Recently, loss of cerebral volume has been proposed as predictive factor in the response to treatment (Pérez-Miralles et al., 2015; Vidal-Jordana et al., 2016, 2015; Cocco et al., 2015), and a vibrant debate has developed around the possible role of cerebral atrophy in daily clinical practice. However, there are still several limitations to this method due to the great variability in methods used and the absence of universally shared definitions (Zivadinov et al., 2016; Wang et al., 2016). Improved knowledge regarding the processes leading to cerebral atrophy could thus be helpful in better understanding the mechanism of MS pathogenesis and establishing a role for brain volume evaluation in clinical

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practice.

Despite the downsizing of the latest diagnostic criteria, analysis of cerebrospinal fluid and IgG oligoclonal bands (OB) detection remain both a fundamental support in MS diagnosis and a possible prognostic factor (Giovannoni, 2014; Gajofatto et al., 2013; Tintore et al., 2015). From the early phases of the disease, in patients with clinically isolated syndrome, the presence of OB is a well-studied risk factor for conversion to clinically defined MS (Dobson et al., 2013; Álvarez-Cermeño and Villar, 2013).

However, the significance of OB in the pathogenesis and prognosis of MS is not yet fully understood. A retrospective case analysis including 100 OB negative MS patients demonstrated that MS patients without IgG-OB in CSF were more likely to show both atypical presentations at onset and better prognoses for physical disability during follow-up when compared with OB positive patients, independently of magnetic resonance (MR) and other clinical features (Joseph et al., 2009).

The aim of this study is to evaluate the relationship between cerebral volumes and OB synthesis in the early phases of MS.

2. Material and methods

2.1. Participant selection

Consecutive MS patients were recruited from March 2015 to March 2016 at the Multiple Sclerosis Centre of the University of Cagliari. The inclusion criteria were: MS diagnosis according to 2010 McDonald Criteria (Polman et al., 2011); clinical onset of MS within 12 months; MRI acquisition and CSF examination simultaneously at inclusion; no other major neurological diseases; no corticosteroid administration in the previous 30 days. All eligible patients without IgG-OB detection were recruited (OB negative group). A control group of patients with OB detection matched for gender, age, and disability was randomly selected by our database (OB positive group). We also recruited a group of healthy controls who underwent the same MRI acquisition in May 2015.

All included subjects signed informed consent form. The study received approval from the local ethics committee.

2.2. MRI acquisition

Brain MRIs were acquired in a single session using a Magnetom Avanto Siemens Scanner at 1.5 T. The MRI protocol included the following sequence: 3D T1-Magnetization Prepared Rapid Acquisition Gradient-Echo (MPRAGE): echo time (TE): 2.37 ms; repetition time (TR): 1730 ms; inversion time (TI): 1050 ms; field of view (FOV): 244 mm; voxel size: 1 × 1 × 1 mm. Brain parenchyma volumes were measured on T1W gradient echo images using the cross-sectional version of SIENA (structural image evaluation using normalization of atrophy) software, SIENAX (part of FSL 4.0: http://www.fmrib.ox.ac.uk/fsl/), and a previously described method to estimate the overall brain volume, normalized for head size. MRI analysis allowed us to obtain normalized brain volume (NBV), normalized grey matter volume (NGV), and normalized white matter volume (NWV) (Smith et al., 2002). T1 hypo-intense lesion refilling was performed as previous described (Battaglini et al., 2012).

2.3. CSF examination

Agarose isoelectric focusing was used to examine OB, combined with immunoblotting and avidin–biotin-amplified double antibody peroxidase staining. Trained readers blinded to both patient identity and clinical and neuro-radiological features assessed the number of CSF-restricted OB. OB positivity was defined as two or more bands present in CSF but absent in plasma at the same point in time.

Table 1
Clinical and demographic features of MS patients included in the study.

	O.B. negative group (20 patients)	O.B. positive group (25 patients)	P value
Age (years)	43.65 (S.D.:11.9)	40.48 (S.D.:12.1)	ns
Gender	F/M: 15/5	F/M: 20/5	ns
EDSS	1.45 (S.D.: 1.23)	2.24 (S.D 1.80)	ns
Disease duration (months)	5.4	5.6	ns

2.4. Statistical analysis

MRI measurements and some clinical variables (age, EDSS, time from onset to lumbar puncture) between groups were compared using T Test for independent samples. Chi square test was used to compare gender between groups. A multivariable linear regression was performed to evaluate the relationship between NWV and OB synthesis adjusting for age, gender and disability.

Results were considered significant when $P \leq 0.05$. Analyses were performed using SPSS 20.0 for Mac.

3. Results

Of 145 patients meeting the inclusion criteria, we recruited all 20 in the OB negative group. A group of 25 patients in the OB positive group was randomly selected. Demographic and clinical features of these patients are shown in Table 1. The means measurements for NBV, NWV, and NGV are shown in Table 2. We also recruited a healthy control (HC) group containing 15 people, the demographic characteristics of which are shown in Table 3. No significant differences regarding age and gender were detected between the HC group and both patient groups.

T test for independent samples showed a significant difference in NWV mean between the OB positive group and the OB negative group ($P = 0.01$). No difference was observed between NBV and NGV in the two groups. T test for independent samples show a significant difference in NWV mean between the OB positive group and the HC group ($P = 0.001$), but not between the OB negative group and the HC group. No difference in NBV and NGV was observed between both groups of patients and the HC group (Table 3).

To evaluate the possible confounding effect of some clinical and demographic variables (gender, age, EDSS), a multivariable linear regression was performed (Table 4). This analysis also confirms the association between synthesis of IgG OBs and reduction in the volume of white matter ($p = 0.02$).

4. Discussion and conclusions

Brain atrophy in MS is the result of pathological processes that include demyelination as well as axonal/neuronal loss. In a large study of MS patients a relationship between the risk of sustained disability and expected brain volume, estimated on the basis of clinical and demographic characteristics, was recently observed (Sormani et al., 2016).

The prognostic role of CSF findings in early phase of MS is well documented. Moreover, the presence of OBs in clinically isolated syndrome predicts both conversion to clinical definite MS and

Table 2
Mean (standard deviation, S.D.) normalized brain volume, normalized white matter volume and normalized grey matter volume in OB negative group and O.B. positive group.

	OB negative group (20 patients)	OB positive group (25 patients)	P value (T Test)
NBV	1517.10 (S.D.: 75.14)	1498.04 (S.D.: 70.57)	ns
NWV	734.10 (S.D.: 68.59)	691.68 (S.D: 38.02)	0.01
NGV	782.93 (S.D.: 80.70)	806.25 (S.D: 50.7)	ns