Cerebrospinal fluid oligoclonal bands and progression of disability in multiple sclerosis

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Antibody-mediated inflammation is believed to contribute to tissue injury in multiple sclerosis (MS). The majority of patients with MS have oligoclonal bands (OCB), corresponding to antibodies against a variety of antigens, in their cerebrospinal fluid (CSF). The relation of CSF OCB and disease progression in MS is uncertain. To investigate whether there is a relation between CSF OCB and a more aggressive disease course of MS, 143 patients with definite MS according to the Poser diagnostic criteria and CSF analysis at time of diagnosis were followed over a period of 5 years. There were no differences in presence or number of CSF OCB between patients with significant worsening of disability and stable patients. There were no differences in presence or number of CSF OCB between patients with stable relapsing-remitting MS and patients developing secondary progression during follow-up. The presence or number of CSF OCB does not seem to influence early disease progression in MS.

Introduction

The disease course in multiple sclerosis (MS) is highly variable; while some patients remain free of disability for a long-time, others quickly deteriorate. One of the most devastating events in MS is the development of a progressive disease course, after which disability no longer worsens in bouts followed by some degree of recovery, but progresses relentlessly.

Cerebrospinal fluid (CSF) analysis shows oligoclonal bands (OCB) in the majority of patients with MS. OCB unique to the CSF argue for an immunologic reaction to a small number of antigens in the intrathecal space. Antibodies that have the capacity to recognize particular targets in the CNS are believed to contribute to tissue injury in patients with MS [1]. Kuhle et al. found increased CSF and magnetic resonance imaging signs of inflammation in patients with CSF antibodies against myelin oligodendrocyte glycoprotein (MOG) and myelin basic protein [2]. Peripheral blood serum antibodies against MOG are especially prevalent in patients with primary progressive MS (PPMS), and have the ability to induce cell death in MOG-expressing cells in vitro [3]. A minority of patients with proven MS have no OCB, and it has been suggested that the patients with this ‘OCB negative’ form of MS may have a better prognosis [4,5]. Furthermore, it has been suggested that a low OCB number in ‘OCB positive’ MS patients predicts a better prognosis [6]. To learn more about the possible influence of CSF OCB on disease progression in MS, we examined the relation between progression of disability over a period of 5 years and CSF OCB in a hospital-based cohort of MS patients.

Patients and methods

Groningen MS database

The Groningen MS database is a prospective database of all MS patients attending the Groningen University Medical Centre (GUMC) MS Clinic, where patients are followed at 3–12 monthly intervals with intercurrent visits if necessary. The GUMC is the main secondary and tertiary referral centre for MS in the province of Groningen (population approximately 575 000). Data acquisition started in 1985, and a diagnosis of definite MS was established according to the Poser criteria [7]. Currently, the database contains clinical data of 672 patients.

Patients

We identified all patients in the Groningen MS database, who had undergone a lumbar puncture as part of their diagnostic workup before the year 2000, and who had not been treated with immunomodulatory or immunosuppressive drugs (with the exception of high-dose steroid courses for the treatment of relapses). We identified 154 patients; 87 with relapsing-remitting MS (RRMS), 15 with secondary progressive MS (SPMS), and 52 with PPMS. During the follow-up period of 5 years, two RRMS patients died because of the causes unrelated to MS and were excluded from the final analysis. Seven
RRMS patients and two PPMS patients were lost to follow-up, leaving 143 patients for the final analyzes.

**Measurements**

Matched CSF and plasma samples were analyzed, during the diagnostic workup, by isoelectric focusing and IgG-specific immunofixation [8]. The presence or absence of OCB unique to the CSF (thus, absent in serum) was reported in all patients, and OCB number was determined in 104. We recorded age, gender, disease duration (the time since the first likely symptom of MS), Expanded Disability Status Scale (EDSS) score at baseline and at follow-up visits. We calculated Multiple Sclerosis Severity Scores (MSSS) from EDSS scores and disease duration as described by Roxburgh et al. [9].

**Clinical end-points**

Clinically relevant worsening of disability during follow-up in all patients was defined as an increase in EDSS score of at least one full point for patients with a baseline score of < 6.0, and at least one half point for patients with a baseline score ≥ 6.0. This definition of relevant worsening of disability was taken from the two main randomized controlled trials on interferon beta therapy in SPMS [10,11]. In view of the possible special relevance of OCB in PPMS patients, we included an analysis on this patient subgroup. In addition, RRMS patients were evaluated for the development of a progressive disease course, defined as the progressive worsening of symptoms for at least one year unrelated to relapses [12].

**Statistics**

Group differences were assessed with the Mann–Whitney U-test and Fisher’s exact test where appropriate. Statistical significance was taken to be at the two-tailed 0.05 level. All statistical analyzes were performed with the spss statistical software package version 12 (SPSS Inc., Chicago, IL, USA).

**Results**

**Progression of disability**

Baseline characteristics of the 143 MS patients are shown in Table 1. Ninety-one (64%) had a clinically relevant worsening of disability during follow-up. The proportion of OCB-positive and OCB-negative patients was not significantly different between worsening and stable patients. OCB number was not significantly different between worsening and stable patients (Table 1). Patients experiencing significant worsening of disability during follow-up were older than patients who remained stable ($P = 0.042$) and had higher EDSS scores at baseline $(P = 0.001)$ (Table 1). There were no statistically significant differences in any variable for the subgroup of PPMS patients (Table 2).

**Development of secondary progression**

Nineteen of the 78 RRMS patients (24%) developed a progressive disease course during follow-up. The proportion of OCB-positive and OCB-negative patients as well as OCB number did not differ between patients developing progression and stable RRMS patients. Patients developing a progressive disease course had significantly higher EDSS $(P = 0.011)$ and MSSS $(P = 0.009)$ scores at baseline than patients who remained relapsing-remitting (Table 3).

**Discussion**

We found no relation between the presence or number of CSF OCB and short-term progression of disability,

| Table 1 Comparison of patients with significant worsening of disability during follow-up and stable patients |
|-------------------------------------------------|-------------------------------|-------------------------|-----------|
| All patients | Significant worsening of disability | Stable disability | $P$       |
| $n$ | 143 | 91 | 52 |       |
| Gender male/female $(n)^a$ | 45/98 | 29/62 | 16/36 | 1 |
| Age at baseline (median, range)$^b$ | 39, 14–71 | 39, 14–71 | 35, 16–68 | 0.042* |
| Years since first symptom (median, range)$^b$ | 2, 0–26 | 2, 0–26 | 2, 0–21 | 0.13 |
| Baseline EDSS (median, range)$^b$ | 3.0, 0.0–7.5 | 3.5, 0.0–6.5 | 2.0, 1.0–7.5 | 0.001** |
| Baseline MSSS (mean, SD)$^b$ | 5, 83, 2.69 | 6, 09, 2.71 | 5.37, 2.61 | 0.076 |
| Oligoclonal bands negative/positive$^c$ | 33/110 | 19/72 | 14/38 | 0.42 |
| Number of oligoclonal bands (median, range) | 3, 0–25$^c$ | 5, 0–25 | 2, 0–17 | 0.11 |

$^a$Fisher’s exact test; $^b$Mann–Whitney test; $^c$Measured in 104 patients (65 with significant worsening of disability, 39 with stable disability).

* $P < 0.05$ ** $P < 0.01$. EDSS, Expanded Disability Status Scale; MSSS, Multiple Sclerosis Severity Score; SD, standard deviation.
indicative of a more aggressive disease course of MS. A possible limitation of our study is the use of the Poser diagnostic criteria, which excludes patients with a single relapse but with MRI findings which would allow a diagnosis according to the McDonald diagnostic criteria. Therefore, our findings can not be generalized to this patient group.

Tintore et al. examined OCB status in 112 patients with a clinically isolated syndrome suggestive of MS. In their study, the presence of OCB had a relatively high sensitivity (0.81), but low specificity (0.43) for predicting the development of definite MS [13]. The importance of OCB in established MS was evaluated by Amato and Ponziani in their cohort study, patients without CSF OCB reached landmark disability scores and developed secondary progression significantly later than OCB-positive patients [5]. These findings are in conflict with our results. Possible explanations for this may be the different end-point measures and the different definition of a progressive disease course used. A previous report by Zeman et al. suggested that OCB-negative MS may have a relatively benign prognosis, but this conclusion was based on the analysis of only 12 patients [4]. In a more recent study by Imrell et al. on 1505 patients, there were no significant differences in MSSS between patients with and without OCB [14].

Avarasala et al. in a study on 44 MS-patients, found a lower number of OCB in patients with EDSS scores of < 3.5 as compared with patients with scores of 7.5 or more, but this difference was not statistically significant [6]. The small patient number, and the use of arbitrary criteria for ‘benign’ versus ‘severe’ MS are weaknesses of their study. Our data suggest that the presence and number of antibodies in the CSF does not influence the disease course of MS.

**Competing interests**

We declare that we have no competing interests.
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References
