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# CORRELATION OF THE IGG INDEX AND OLIGOCLONAL BANDS IN THE CEREBROSPINAL FLUID OF PATIENTS WITH MULTIPLE SCLEROSIS

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**Aims**: The aim of this study was to assess the correlation between IgG index values and the number of the oligoclonal IgG bands (OCB) in the cerebrospinal fluid (CSF) of patients with multiple sclerosis (MS).

**Material and Methods:** The set of 150 patients consisted of 41 males and 109 females (aged 18–68, mean 36.6 ± 10.1 years). The CSF collected by a lumbar puncture was examined evaluating intrathecal synthesis using the IgG index and determining OCB. The number of alkaline OCB in the CSF was assessed using the method of isoelectric focusing. Pearson's correlation analysis, and homogeneity $\chi^2$ test, Mann-Whitney test, paired-sample t-test (parametric) and Wilcoxon signed-ranks test (nonparametric) were used to evaluate the statistical significance of the results.

**Results**: No positive correlation between the IgG index and the number of OCB was found. Mann-Whitney test also failed to demonstrate any significant difference of the IgG index values in patients both with the OCB number $\geq 2$ and $< 2$.

**Conclusion**: This study did not confirm any correlation between the IgG index values and the OCB number in the CSF of MS patients.

## INTRODUCTION

Immunoglobulins are glycoproteins produced by plasmocytes. In contrast to the known and characteristic reaction in the serum, where antibody production switches from the IgM to IgG class in the subacute and chronic phase of the disease, such a transition is not present in the intrathecal synthesis. The characteristic immunoglobulin pattern in classes IgG, IgM and IgA existing in the central nervous system (CNS) remains relatively constant from the disease onset. Intrathecal IgG synthesis represents local IgG production within the CNS compartment, originates from perivascular infiltrates of B lymphocytes. Quantitative assessment of the intrathecal IgG synthesis is based on the relationship between IgG and albumin concentrations in the CSF and serum. Oligoclonal IgG immunoglobulins represent a primarily polyspecific and only subsequently an oligoclonal type of immune response. This produces an extensive spectrum of non-specific antibodies of "nonsense" nature.

In many countries, information obtained from detailed assessment of the CSF is currently important in the MS diagnostics. In all MS stages, increased IgG levels, which after correction for the function of the blood-brain barrier show intrathecal synthesis, can be found. It is possible to demonstrate this as OCB by which the immunoglobulins participating in the destruction of the myelin covering of axons line up to special patterns. OCB assessment is the most specific CSF test for MS diagnosis[1] – their presence supports this diagnosis as they are not found in the serum of these patients and are therefore a proof of antibody production directly in the CNS. OCB are present (as 2 or more) in the CSF of 95–100 % of MS patients[2, 3]. In 40 % of MS patients, OCB may be found in the serum as well. OCB can be present even in the case, when the CSF IgG level is normal. Finally, these bands are not specific to for MS – they are also found in various inflammatory disorders as well as in chronic CNS infections. On the other hand, they are not present in neurodegenerative diseases, acute disseminated encephalomyelitis, Guillain-Barré syndrome, toxic, metabolic, traumatic or psychiatric disorders, radicular syndromes or in the majority of peripheral neuropathies[4]. OCB have a predictive value in the case of a negative magnetic resonance imaging finding (MRI), but there is no direct correlation between the OCB in the CSF and the demyelinating process as assessed by the MRI.

Treatment for the relapsing-remitting MS with beta-interferons and glatiramer acetate leads to significant decrease in the number of relapses and to the shortening of their duration as well as to a slower worsening in the MRI findings. Only limited data on the immunological CSF findings during the disease-modifying drug (DMD) therapy has been published in the current literature and the changes in OCB patterns have mostly not been described[5].

The aim of this study was to assess the correlation between IgG index values and the OCB number in the CSF of patients with MS.

**Table 1.** IgG Index values.

| IgG Index | Frequency | Percent | Valid Percent |
|---|---|---|---|
| <= 0.7 | 91 | 60.7 | 61.9 |
| > 0.7 | 56 | 37.3 | 38.1 |
| Total | 147 | 98.0 | 100.0 |
| Unlisted | 3 | 2.0 | |
| Total | 150 | 100.0 | |

**Table 2.** Number of oligoclonal IgG bands.

| IgG Index | Frequency | Percent | Valid Percent |
|---|---|---|---|
| >= 2 | 97 | 64.7 | 70.3 |
| < 2 | 41 | 27.3 | 29.7 |
| Total | 138 | 92.0 | 100.0 |
| Unlisted | 12 | 8.0 | |
| Total | 150 | 100.0 | |

## MATERIAL AND METHODS

The sample of 150 MS patients consisted of 41 males and 109 females (aged 18–68, mean 36.6 ± 10.1 years). The diagnosis of RRMS was established based on the McDonald's criteria. All patients were treated at the Department of Neurology, University Hospital, Olomouc, Czech Republic, between 2001 and 2005.

In all patients, the CSF was collected by routine lumbar puncture as part of the standard diagnostic process. The assessment of the IgG index and of the OCB was used for the evaluation of the intrathecal synthesis. IgG method of Pharmacia Biotech (Uppsala, Sweden) modified for using of acrylamid gel PhastGel ICF 3–9 and by isoelectric focusing (IEF) (ref.[6]) with successive affinity immunoblot was used. The number of OCB in the CSF was assessed by the method of isoelectric focusation (IEF). The samples were examined in a laboratory with an international certificate for the IEF method (KB/0079).

Pearson's correlation analysis, and homogeneity $\chi^2$ test, Mann-Whitney test, paired-sample t-test (parametric) and Wilcoxon signed-ranks test (nonparametric) were used to evaluate the statistical significance of the results, using SPSS-10 software package (SPSS, Chicago, USA). Sensitivity and specificity of the IgG index and the OCB number for the prediction of MS diagnosis were also assessed.

The study was conducted in accordance with the Helsinki Declaration of 1975 (as revised in 1983) and it was approved by local ethics committee of University Hospital in Olomouc, Czech Republic.

## RESULTS

Only OCB present in the CSF and absent from serum were considered. IgG index and the OCB number are summarized in the Tables 1 and 2.

No positive correlation between the IgG index and the number of OCB was found by the Pearson´s correlation and nonparametric Spearman correlation. Using the Mann-Whitney also test did not demonstrate any significant difference of the IgG index values in patients both with the OCB number ≥ 2 and < 2.

We also determined the sensitivity and the specificity of the technique used in our laboratory: characteristics of diagnostic test of IgG index >0.7 for prediction of MS diagnosis: sensitivity – 38.1 %, specificity – 91.7 %, accuracy – 77.6 %, positive predictive value – 62.2 %, negative predictive value – 80.5 %. Characteristics of the diagnostic test of OCB number >=2 for prediction of MS diagnosis: sensitivity – 70.3 %, specificity – 76.1 %, accuracy – 74.4 %, positive predictive value – 53.3 %, negative predictive value – 86.8 %. Characteristics of the diagnostic test both of of IgG index >0.7 and oligoclonal IgG bands number >=2 for prediction of MS diagnosis: sensitivity – 77.0 %, specificity – 73.7 %, accuracy – 74.6 %, positive predictive value – 51.1 %, negative predictive value – 90.0 %.

## DISCUSSION

The dynamics of the appearance and the development of OCB during the course of MS is not yet generally known[7]. In the study performed by Kaiser et al.[8], only two cases (1 %) out of the 185 CSF samples obtained from MS patients demonstrated specificity of OCB antibodies against known CNS antigens. Rudick et al.[5] found

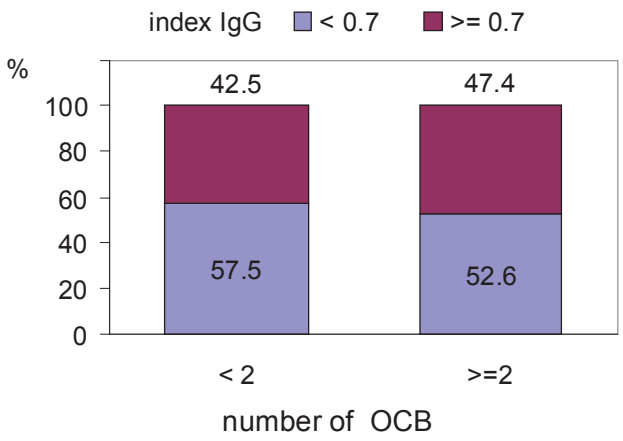


**Fig. 1.** Correlation of the IgG index a OCB number

no changes in the IgG index, light kappa chains or OCB patterns in 137 repeated CSF samples and 2 years after the beginning of Avonex therapy. Kinnunen et al.[9] found that in 3 (50 %) out of the 6 patients with progressive MS, alfa-interferon therapy lead to increased intrathecal synthesis and production of OCB. Livrea et al.[10] found no correlation between the OCB pattern or amounts and age, duration, clinical course or therapy of the disease.

Concerning to correlation between the IgG index and OCB there is a lack of data in the current literature – Kaiser et al.[11] used two quantitative methods of determining the intrathecal synthesis of IgG for their usefulness in deciding about the necessity of further investigations of OCB in the CSF. While OCB could be detected in no patient with an IgG index < 0.45, OCB were always demonstrated in patients with an index > 0.80. Even though a range of 0.45–0.8 OCB was only detected in 268 out of 1316 patients (20.4 %), in 190 out of 268 samples (70.8 %) OCB were the only criterion for intrathecal synthesis of IgG. OCB were always detected if local production of IgG was > 12 %. In Anderson[12] et al. study, CSF IgG index fell significantly with initial methylprednisolone treatment of 26 MS patients and significant reductions in CSF IgG, CSF albumin, serum IgG and serum albumin levels and CSF IgG synthesis rate in the first and repeat treatment groups were described. Mayringer et al.[13] investigated if there is a correlation between the frequency of OCB and the IgG index and if the IgG index predicts the diagnosis of a demyelinating CNS disease. They found a positive correlation between the IgG index and the frequency of OCB as well as the probability of demyelinating CNS disease.

In contrast we found no positive correlation between both parameters of intrathecal synthesis. In accordance with our findings, Rochelli et al.[14] reported 63 out of 70 patients with definite MS and 24 out of 35 with probable MS had oligoclonal bands in the CSF and in the 18 patients with normal OCB pattern no statistically significant difference was found in the quantitative CSF parameters (IgG index, IgG synthesis and serum/CSF albumin quotient) compared to the patients with the OCB in CSF. Also in Poloni[15], in a group of 120 MS patients a group of 20 patients with normal IgG profile were compared with a group of 22 patients selected by random out of 100 with IgG oligoclonal bands and no statistically significant difference was discovered between these groups.

## CONCLUSION

This study found no correlation between the IgG index values and the OCB count in the CSF of MS patients. Further studies are needed to clarify the issue.

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