Relapsing-remitting Multiple Sclerosis and Oligoclonal Band Pattern During Disease Modifying Drug Therapy

Relabující-remitující roztroušená skleróza a oligoklonální pruhy v průběhu léčby modifikující průběh choroby

Abstract

The aim of this study was to assess oligoclonal bands (OCB) in the cerebrospinal fluid (CSF) in patients with relapsing-remitting multiple sclerosis (RRMS) treated with disease modifying drug (DMD) therapy. The authors examined a group of 22 patients, 5 males (aged 19–44, mean 29.8 \pm 6.5 years) and 17 females (aged 26–51, mean 37.8 \pm 6.7 years). CSF samples were taken 0–42 months before and 1–16 months after the initiation of DMD therapy. The number of OCB in the CSF was assessed by isoelectric focusing. Paired sample t-test and Wilcoxon signed-rank test were applied when assessing statistical significance. In the patient group, the number of OCB at follow-up decreased significantly (mean decrease 6.2, median 3.5, p = 0.001, paired t-test). These results demonstrate changes in OCB patterns, respectively support the hypothesis about possible immunomodulation effect of DMD therapy.

Souhrn

Cílem studie bylo vyhodnotit oligoklonální pásy (OCB) v mozkomíšním moku (CSF) u pacientů s relapsující remitující roztroušenou sklerózou (RRMS) léčených nemoc modifikujícími léky (DMD). Autoři vyšetřili skupinu 22 pacientů, z nichž bylo 5 mužů (ve věku 19–44 let, průměrný věk 29,8 \pm 6,5 let) a 17 žen (ve věku 26–51 let, průměrný věk 37,8 \pm 6,7 let). Vzorky CSF byly odebrány 0–42 měsíců před a 1–16 měsíců po zahájení DMD léčby. Počet OCB v CSF byl stanoven metodou izoelektrické fokusace. K vyhodnocení statistické významnosti byl použit párový t-test a Wilcoxonův jednovýběrový test. V pacientské skupině se počet OCB při sledování významně snížil (průměrný pokles byl 6,2, medián 3,5, p = 0,001, párový t-test). Tyto výsledky prokazují změny vzorců OCB, respektive podporují hypotézu o možném imunomodulačním účinku DMD léčby.

J. Mareš¹, R. Herzig¹, K. Urbánek¹,

- J. Podivínský⁵, V. Bekárek²,
- J. Sklenařová², J. Zapletalová³,
- P. Hluštík¹, V. Sládková¹,

D. Doležil⁴, P. Kaňovský¹

¹Department of Neurology,

- LF UP a FN Olomouc
- ² Department of Clinical Biochemistry, LF UP a FN Olomouc
- ³Department of Biometrics, LF UP a FN Olomouc
- ⁴ Department of Neurology, University Hospital Ostrava-Poruba
- ⁵Neurology Geriatric Medical Institution, Moravský Beroun

\square

MUDr. Jan Mareš

Centrum pro diagnostiku a léčbu demyelinizačních onemocnění Neurologická klinika LF UP a FN I. P. Pavlova 6, 775 20 Olomouc e-mail: maresja@seznam.cz

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Klíčová slova

oligoklonální pásy – mozkomíšní mok – interferon beta – roztroušená skleróza

Introduction

The detailed assessment of the CSF is currently a part of multiple sclerosis (MS) diagnostics. In all stages of this disease, we can find increased IgG levels in CSF which after correction for the function of the bloodbrain barrier show its intrathecal synthesis. It is possible to demonstrate it as OCB. OCB represent immunoglobulin fractions participating in myelin destruction. OCB detection by isoelectric focusing is the most specific CSF test for MS [1] - it provides a significant support for MS diagnostics because they are not usually found in the serum of these patients and are therefore a proof of antibody production directly in central nervous system (CNS). OCB in the alkaline area are by CSF assessment positive (2 or more bands) in 95-100% of patients with MS [2, 3, 4]. In 40% of MS patients, OCB may be found in the serum as well.

OCB can be present even when the CSF IgG level is normal. Finally, these bands are not specific only for MS - they are also found in various inflammatory disorders as well as in chronic infections of the CNS, in acute disseminated encephalomyelitis [5], Guillain-Barré syndrome [6] or neurodegenerative dementia [7], vascular, toxic, metabolic, traumatic or psychiatric disorders, radicular syndromes or in most peripheral neuropathies [8]. The finding of oligoclonal bands in the CSF almost doubles the risk of develop in clinically definite MS [9]. OCB have a predictive value in the case of negative MRI but there is no direct correlation between OCB in the CSF and the demvelinating process as assessed by the MRI.

Therapy of RRMS with interferons leads to a significant decrease in the number of relapses and to a shortening of their duration as well to marked improvement of MRI findings. There are only limited data concerning immunological CSF findings during the interferon therapy in the current literature and changes of OCB patterns mostly have not been described [10].

The aim of the study, which has been realized at the Department of Neurology, University Hospital in Olomouc, Czech Republic, was to find out whether OCB number changes during the DMD therapy. We tried to investigate whether there are changes in the OCB patterns during the DMD therapy.

Subjects and Methods

The studied patient group (N = 22) consisted of 5 males (aged 19–44, mean 29.8 \pm 6.5 years), and 17 females (aged 26–51 years, mean 37.8 \pm 6.7 years). The diagnosis of RRMS was established based on the McDonald's criteria [11].

The CSF was collected by a routine lumbar puncture as part of the standard diagnostic process prior to the start of the DMD therapy (0–42 months before, mean 13,5 \pm \pm 8,2) and for a second time (after receiving informed consent) 1–16 (mean 6,2 \pm 2,1) months after the beginning of the DMD therapy. During the study, some patients were treated with immunosupressive therapy (Imuran p.o.) or chronic steroid therapy (Medrol p.o., Prednison p.o.). Relapses were treated with bolus of steroids (5g Solu-Medrol i.v.) – see Table 1.

The method of Pharmacia Biotech modified for using of acrylamid gel PhastGel ICF 3–9 and by isoelectric focusing (IEF) with successive affinity immunoblot was used. The number of OCB in the CSF was assessed by the method of isoelectric focusing in a laboratory with the certificate KB/0079, which was blinded to the aim of this study and to the patient's therapy.

Paired-sample t-test (parametric) and Wilcoxon signed-ranks test (nonparametric) were applied when assessing statistical significance, using SPSS-10 software package (SPSS, Chicago, USA).

The whole 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

The numbers of OCB before immunomodulation treatment and after the initiation of DMD therapy are summarized in Table 1 and Figure 1.

Only OCB bands present in the CSF and absent in serum were considered. In 18 patients, a reduction in the number of OCB was observed (mean 7.8 \pm 5.9), in 2 patients the number of OCB increased by 1 and 3 (mean 2 \pm 1) and in 2 patients there were

no changes in the number of OCB. In several patients, a regression from 8 to 1 OCB was observed. Overall, the number of OCB between 1st and 2nd examination at follow up decreased significantly (mean 6.2, median 3.5; p = 0.001, paired t-test), see Figure 1.

Considering that the distribution of OCB counts is asymmetrical with lower bound of 0, statistical significance was confirmed using a nonparametric Wilcoxon signed-ranks test (p = 0.0004). Sensitivity for MS prediction was 90.9, specificity 76.1 and negative predictive value 99.3.

Discussion

OCB represent the set of antibodies against yet unknown antigens of the CNS, probably of "nonsense" nature. The dynamics of the appearance and the development of OCB during the course of MS is not generally known yet [12]. In the study by Kaiser et al. [13], only two cases (1%) out of the 185 CSF samples obtained from patients with MS demonstrated the specificity of OCB antibodies against known CNS antigens. Rudick et al. [14] did not observe any changes in the IgG index, light kappa chains nor OCB patterns in 137 repeated samples of CSF before and 2 years after the beginning of Avonex therapy. Administration of interferon beta intrathecally (i.t.) for duration of 2 months did not lead in study by Confavreux et al. [15] in 11 patients after 6 months to OCB change. On the contrary, a characteristic individual "fingerprint" of the OCB in the CSF was preserved, allowing recognition of the patient to whom the CSF sample belonged. Saiz et al. made similar observations in MS patients who underwent an autologous hematopoietic stem cell transplantation the baseline CSF OCB persisted for 1 year following transplantation [16]. Kinnunen et al. [17] have found that in 3 out of the 6 patients with progressive MS, alfa-interferon therapy lead to increased i.t. synthesis and production of OCB.

Other studies [18–20] described the changes of OCB during the steroid and Cladribin therapy where the changes observed in the CSF banding pattern were not significant. On the basis of the above-mentioned findings, it is possible to note that during

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4.	ш	40	29	XI-02	VII-03	XI-02	Betaferon	0	∞	lm 25	Med 16	0	lm 50	Med 8	0	12	4
5.	ш	46	00	XI-02	VII-03	XI-02	Betaferon	0	∞	lm 25	Med 4	-	0	0	0	ω	0
.9	Σ	29	2	IX-01	XII-02	X-02	Betaferon	13	2	0	Med 4	0	0	Med 4	0	22	4
7.	ш	34	m	00-VI	IV-02	XI-01	Avonex	19	S	lm 25	Med 4	0	0	Med 8	0	12	12
œ.	щ	51	14	VII-01	XI-02	IV-02	Betaferon	6	7	0	0	-	0	0	0	ß	4
б	ш	49	27	00-VI	XI-02	IV-02	Copaxone	24	7	0	0	-	0	0	-	14	0
10.	щ	43	5	VI-01	III-03	II-03	Avonex	20	-	0	Med 32	-	0	0	0	m	0
11.	ш	34	-	00-VI	IX-01	IV-01	Rebif 22	12	ъ	lm 25	Pred 5	-	lm 50	Pred 5	0	12	9
12.	Σ	19	-	00-IX	XI-01	IV-01	Betaferon	Ŀ	7	0	0	-	0	1	0	11	∞
13.	щ	39	23	00-II/	XI-01	IV-01	Copaxone	6	7	0	Pred 20	-	0	Pred 20	0	23	0
14.	ш	26	4	X-98	XI-01	IV-02	Rebif 44	42	7	0	0	0	lm 25	Med 16	0	20	0
15.	ш	37	18	00-I/	V-02	1-01	Rebif 22	7	16	0	Med 16	0	0	0	0	16	17
16.	Σ	44	-	00-11	XI-01	VII-01	Betaferon	17	4	0	Pred 5	-	0	Med 8	0	. 	0
17.	ш	46	m	00-III	XII-02	IV-02	Avonex	25	б	0	0	0	0	Med 8	0	16	0
18.	ш	46	2	00-III/	XII-02	IV-02	Copaxone	20	∞	0	0	0	0	0	. 	12	∞
19.	ш	26	2	I-01	I-02	VII-01	Avonex	9	9	0	0	0	lm 50	Pred 10	. 	21	20
20.	Σ	32	-	VII-03	II-04	X-03	Avonex	m	4	lm 25	0	-	0	0	0	9	2
21.	ш	32	m	IV-03	II-04	X-03	Betaferon	9	4	lm 50	Pred 10	-	lm 25	Med 4	0	0	0
22.	ш	29	-	VI-00	X-01	IV-01	Rebif 22	10	9	0	0	0	lm 50	Med 16	1	17	16
inv. – ir	ivestigati	inv. – investigation (CSF assessment), immunosupress. – immunosupr	sssment), im	munosupre	ss. – immur	tosupressive	essive therapy, Im – Imuran, Pred – Prednison, Med – Medrol	- Imuran, Pr	ed – Prednis	son, Med – M	tedrol						

RELAPSING-REMITTING MULTIPLE SCLEROSIS AND OLIGOCLONAL BAND PATTERN DURING DISEASE MODIFYING DRUG THERAPY

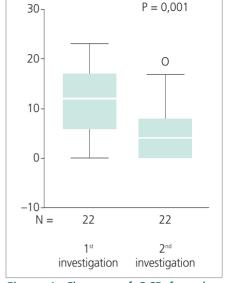


Figure 1. Changes of OCB from between the 1st and 2nd examinations.

DMD therapy, the number of OCB in the CSF may change – in our group of patients we found a tendency to decrease or disappeareance of OCB - similar findings were described in study of Andersonn et al. [14] who found disappeareance of OCB during methylprednisolone treatment of MS patients in 3 patients out of the 45. The disappearance of OCB was described in patients with other autoimmune neurological diseases - in study of Bergamaschi et al. [21] OCB have been found in 3 of 11 patients with Devic's neuromyelitis optica and by repeated CSF assessment always disappeared. The results in our study showed significantly decreased numbers of OCB, but this study has some limitations: firstly, the group of patients was relative small with absence of control group (patients with RRMS without DMD therapy constitute an ethic problem). Secondly, the possible influences of bolus of steroids in relaps of MS and immunosupressive therapy - can accelerate the suppression of inflammatory process and oligoclonal syntesis. Thirdly, the pathogenesis of OCB in MS is still obscure and the final picture of oligoclonal syntesis is based on manifestation the different participations both of T-cells and B-cells on autoimmune response with a variability in intrathecal syntesis. The emphasis on T cells has derived from the detection of activated T cells in MS plaques. Currently the role of B cells, plasma cells and immunoglobulins in MS have been re-examined. and findings indicate that humoral immunity also plays a major role in MS pathogenesis. According to Coreale et al. [3], B cells and their products could exert several potential effects during the course of MS autoantibodies against specific myelin antigens could mediate damage to myelin membranes, some studies suggest that natural autoantibodies could enhance remyelination, antibodies directed against myelin components can participate in anti-idiotypic networks, which may regulate the course of MS. Therefore, a critical task is to clearly desribe this issue and follow-up studies are necessary considering the patophysiological aspects of OCB changes in MS.

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