Retinal periphlebitis in patients with multiple sclerosis

Retinalni periflebitis kod bolesnika sa multiplom sklerožom

Miroslav Stamenković*, Dragana Obradović†

*University Medical Center Zvezdara, Eye Clinic, Belgrade, Serbia; †Military Medical Academy, Clinic for Neurology, Serbia, Belgrade

Abstract

Background/Aim. Multiple sclerosis (MS) is an immune-mediated disorder of the central nervous system (CNS), characterized by inflammation, demyelination and axonal loss. Retinal periphlebitis (RP) is often present in MS patients with similar evolution and histopathological changes as MS lesions. The aim of this study was to analyze the presence of RP in MS patients during different clinical phases, and its connection with impairment of blood-brain barrier. Methods. The study included 45 patients (26 females and 19 males) with MS. Their average age was 33.2 ± 8.1 years. There were 28 patients with relapsing-remitting (RR) form, 7 with primary progressive (PP) and 10 with secondary progressive (SP) form of MS. There were 27 patients in the relapse and 18 patients in the remission phase. The average MS duration was 7.48 ± 1.3 years. Ophthalmological, neurological and MRI examination were performed in all the patients, as well as cerebrospinal fluid sampling. Albumin ratio and IgG index were calculated in all the patients.

Results. There were 9 patients with RP, and 36 without it. MS duration was significantly longer in the RP group. RP was much more common in the progressive form and was not present in the remission phase of MS. Albumin ratio values were increased in the group with RP. IgG index and IgG synthesis according to Tourtellotte formula, were statistically higher in the group of patients with RP. The values of visual evoked potentials (VEPs) latency were significantly higher in the group of patients with RP. The presence of RP is a reliable indicator of MS activity and might be considered as a parameter for monitoring the disease activity and effects of the treatment.

Key words: multiple sclerosis; phlebitis; retinal diseases; diagnosis; prognosis.

Introduction

Multiple sclerosis (MS) is an immune-mediated disorder of the central nervous system (CNS) which is characterized by inflammation, demyelination and axonal loss. The most common course is relapsing-remitting (RR) with unpredictable duration of remissions and frequency of relapses. In time, the majority of patients with RR form of MS turn into secondary progressive (SP) form, though in a smaller sample of patients the course might be primary progressive.
from the very beginning. MS is a disease of younger population, with age prevalence between 20 and 40 years. Females are more often affected and in time MS results in a severe neurological and functional disability and disability 1.

The basic pathological findings are demyelinated plaques in white matter, especially periventricular localization, cervical spine and optical nerve. Disseminated plaques are infiltrates around blood vessels. Similar perivascular infiltrates are found around blood vessels of the retina, the most commonly around veins 2. Rucker was the first to describe the changes in blood vessels in patients with multiple sclerosis. Today, it is believed that veins of retinal periphery are affected by the same pathological process as in MS 3–7. Inflammation may be localized on the larger retinal veins as well. The disorder is characterized by focal and diffuse vein sheathing (Rucker’s sign), sheathing centered on sites of arterial venous crossover, focal perivenuous hemorrhage 8 and perivascular gliosis 9. Active vascular disease is characterized by white exudates of round or oval contours around retinal veins resulting in white sheathing or cuffing of the affected vessels 10. Blood vessels of retinal periphery show the sheathing, narrowing of lumens, while the inadequate perfusion of the retinal periphery induces the progress of degenerative changes in the periphery, appearance of retinoschisis, ruptures, thrombosis of blood vessels, consequently ischemia and neovascularisation in the occlusive forms of periphlebitis 11–13. Retinal periphlebitis (RP) occurs in discrete episodes and often relapses, it is frequently bilateral, and may affect one or multiple retinal veins. The disorder of peripheral retinal blood vessels is not in correlation with the impairment degree of the optic nerve 17. However, the disorder of blood vessels in peripapillar and perimacular region may cause the development of cystoid macular edema 15–17. Cases of association of periphlebitis with anterior uveitis and cystoid macular edema have been described 18–21. The pathological substrate of retinal venous inflammation, i.e. RP is identical to the one existing in the CNS of MS patients which is characterized by perivascular infiltration of lymphocytes and plasmocytes 22–24. The evolution of RP is relapsing, similar to the evolution of changes occurring in the CNS of MS patients 25–27. Changes in retina, including inflammatory processes, may represent the indicators of generalized inflammatory response of the CNS during the course of MS.

There are few studies related to the presence of RP in MS patients 28–32. However, to the best of our knowledge there is no data concerning correlation of RP and MS type, neurological disability and cerebrospinal fluid (CSF) parameters.

In regard to this, the aim of the study was to investigate the presence of RP in MS patients, to investigate the correlation between MS type and RP presence, as well as correlation between RP and disease severity, CSF and MRI parameters.

Methods

The study included 45 patients with the established diagnosis of MS according to Poser criteria 33. All the patients were examined and treated in the Department of Neurology, Military Medical Academy, Belgrade. The patients were examined by the same neurologist, neurological exam was scored by using Expanded Disability Status Scale (EDSS) 34. According to MS course, all three types of MS were present: RR, SP and PP. In relation to present disease activity, the patients were divided into the remission, relapse and progressive group. All the patients were examined by the same ophthalmologist for the presence of RP. The direct ophthalmoscopy (Goldmann’s three-mirror lens) were used for diagnosing RP. According to the presence of RP (Figure 1), the patients were divided into two groups.

CSF sampling was performed by lumbal puncture in all the patients. Following analyses were performed: CSF protein levels, CSF and serum albumin and IgG levels. Albumin ratio, a marker of blood-brain barrier damage, was calculated (cerebrospinal fluid albumins/serum albumins), normal range considered to be < 5.7.

In order to determine intrathecal IgG synthesis as a marker of immunological activity within the CNS, IgG index

was calculated [IgG CSF: IgG serum (albumin CSF/albumin serum)], as well as intrathecal IgG synthesis by using a modified Tourtellotte’s formula 35.

Brain MRI was performed in all the patients within the three days of neurological and ophthalmological examination. It was performed on MRI General Electric 0.5T in the Department of Radiology, Military Medical Academy, Belgrade. In all the patients brain MRI scans were performed with and without Gadholmium (Gd) contrast according to standardized recommended procedure 36, 37. The presence of Gd+ lesions on MRI scans was considered as marker of blood-brain barrier damage.

Visually evoked potentials (VEP) were performed in standard way 38, 39 in the Department of Neurophysiology, Military Medical Academy, Belgrade. According to our control group, amplitude values from 4.5 to 10 μV were considered normal while latency values from 90 to 110 ms were considered as normal. The values of the amplitude below normal were regarded as the parameter of disease activity.

The average and standard deviations were calculated for all parameters of observation, and the significance of differences was determined by Student’s t-test. For non-parametric characteristics of observation, the frequency was registered, and the importance of differences was determined by χ² test. Regarding small specimens, Fischer’s test of precise probability was used. In both cases if the value of p was less than 0.05, the difference was considered statistically significant.

Results

This study included 45 patients with the established diagnosis of multiple sclerosis (26 females and 19 males). The average age was 33.2 ± 8.17 years. In regard to MS type, there were 28 patients with RR form, 7 with PP and 10 with SP form of MS (Table 1). There were 27 patients in the relapse phase and 18 patients in the remission phase.

The average duration of MS was 7.48 ± 1.347 years in the study group.

On the basis of RP presence, all the patients were divided into two groups: with RP there were 9 patients, and without the RP 36 patients. MS duration was longer in the group of patients with RP (9.77 ± 1.81 years), than in the group without RP (6.91 ± 1.305 years), and this difference was statistically significant (p < 0.05). This result indicates that the longer duration of the disorder causes more severe inflammation.

RP was much more common in the progressive forms of MS, SP and PP, compared to RR form of MS (p < 0.001, Fisher’s test Ho p = 0.00003) (Table 1). RP was not found in the remission phase of MS.

In the group with RP visual acuity was on average 0.79, while in the group without RP visual acuity was on average 0.90. In the whole group visual acuity on average was 0.87.

Albumin ratio values were increased in the group with RP (normal range < 5.7) and within the normal range in the group of patients without RP (Table 2), thus there was a statistically significant difference between albumin ratio values between the two groups. (p < 0.001) (Table 2).

Also, CSF protein level was significantly higher in the group of patients with RP compared to the group without RP (p < 0.001) (Table 2). In the group without RP, CSF protein levels were within the normal range (< 0.45 g/l), while in the group with RP CSF protein level was increased.

Table 1

| Presence of retinal periphlebitis (RP) according to gender and multiple sclerosis (MS) type |
|----------------------------------|------------------|
| Gender and MS type | Patients (n) with RP | Patients (n) without RP |
| Gender | | |
| male | 4 | 15 |
| female | 5 | 21 |
| MS type | | |
| remittent-relapsing form | 0 | 28 |
| primary and secondary-progressive form | 9 | 8 |

Table 2

The average and SD values of IgG index, number of cells, intrathecal IgG synthesis (Tourtelotte), albumin ratio, CSF protein levels and types of lesions on MRI in the group of patient with and without retinal periphlebitis (RP)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Patients with RP</th>
<th>Patients without RP</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG index, ³ ± SD</td>
<td>1.388 ± 0.422</td>
<td>0.824 ± 0.495</td>
</tr>
<tr>
<td>Number of cells, ³ ± SD</td>
<td>3.778 ± 2.635</td>
<td>2.7 ± 1.4</td>
</tr>
<tr>
<td>De novo intrathecal IgG synthesis, ³ ± SD</td>
<td>26 ± 20.27</td>
<td>9.58 ± 13</td>
</tr>
<tr>
<td>MR lesions (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>old</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>fresh and old</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>Albumin ratio, ³ ± SD</td>
<td>7.55 ± 0.831</td>
<td>4.94 ± 2.14</td>
</tr>
<tr>
<td>CSF protein levels (g/L), ³ ± SD</td>
<td>0.556 ± 0.08</td>
<td>0.344 ± 0.125</td>
</tr>
</tbody>
</table>

MRI – magnetic resonance imaging; CSF – cerebrospinal fluid

The result was indicative of the active inflammatory response of the CNS.

Comparing the average values of the number of cells, it was found out that they were statistically much higher in the group of patients with retinal periphlebitis ($p < 0.01$) (Table 2).

Both parameters of intrathecal IgG synthesis, IgG index and IgG synthesis according to Tourtelotte formula, were found to be statistically higher in the group of patients with RP ($p < 0.001$) (Table 2). At the same time, intrathecal IgG synthesis was increased only in the group with RP, since IgG index and IgG synthesis according to Tourtelotte formula were above the normal range (0.7 and -3.3–9.9, respectively) in this group.

In regard to MRI lesions, it was found that Gd+ lesions were much more common in the group of patients with RP ($p < 0.025$, Fisher’s test $H_0 = 0.012$) (Table 2).

The values of VEP’s latency were significantly higher in the group of patients with RP, in comparison to the group without RP (Table 3), at the same time the values of VEP’s amplitude was found to be significantly lower in the group of patients with RP (Table 3).

### Table 3

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Patients with RP</th>
<th>Patients without RP</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEP amplitude ($\mu$V)</td>
<td>3.177 ± 1.307</td>
<td>5.732 ± 3.704</td>
</tr>
<tr>
<td>VEP latency ($\mu$V)</td>
<td>148.5 ± 19.27</td>
<td>131.208 ± 24.01</td>
</tr>
</tbody>
</table>

**Discussion**

In our study, the occurrence of RP was 20% (9 patients). In previous studies, data varies from 5.9% to 36% $^{29–31, 40–42}$. The differences in the reported incidence of RP in various studies are first of all due to different interpretation of changes in the retina (all changes are explained in terms of periphlebitis or only as Rucker’s sign) $^{43}$. The differences are caused by the choice of subjects, monitoring time, as well as by MS type and MS presentation – relapse or remission. Longer monitoring, as well as the more severe forms of MS give rise to much more common occurrence of RP. Due to peripheral localization of the changes and the possibility that they are not to be detected in narrow iris, it is required to perform the examination in maximal mydriasis, which on the other hand may diminish the frequency of RP in the patients with MS. There were five females and four males in the group of patients with RP. The periphlebitis was bilateral in four patients, and in five patients, it occurred only unilaterally. In the literature available to us, we found out data on both eyes being affected in patients with multiple sclerosis only in the reports on individual cases. Therefore, we cannot correlate the data with other studies. We would like to stress that if both eyes are affected, it indicates neurological progression and worse clinical prognosis of MS $^{5, 15}$. These patients developed SP form of MS. In the group of patients with RP all the patients had either primary (four patients) or secondary (five patients) progressive form of MS, and neither had RR form of the disease. This is in accordance with certain studies affirming the correlation between the presence of these changes and clinical evidence of the MS progression $^{5, 15}$. We consider that the differences in the study results are due to the way in which the subjects were chosen, and to the monitoring time. In the whole group of patients, RP as the initial mark of the disorder occurred in one case, first in one eye then in the other (11.5%). In relation to the very beginning of disorder, periphlebitis occurred on average after 4.22 years, which was in accordance with the data from the literature $^{11, 29}$. Longer duration of the disorder causes the more severe extent of inflammation and evolution of RP.

Minor differences in the visual acuity between the group of patients with and without RP are mainly caused by peripheral localization of retinal changes $^{19, 42, 44}$. The RP was an initial symptom of multiple sclerosis in one patient (2.22%). These data are in accordance with the data from the literature $^{29, 45–47}$. Our research detected statistically higher values of albumin ratio in the group of patients with RP, which is in accordance with the data from the literature $^{48, 49}$. This finding indicates the blood-brain barrier impairment, i.e. active inflammation within the CNS. Moreover, in the same group MRI Gd+ were much more common ($p < 0.001$) compared to the group without RP (Table 2). Both parameters indicated a blood-brain barrier damage in the group of MS patients with RP, while in non RP group blood-brain barrier was intact. In previous studies, no relation was found between the damaged blood-brain barrier and presence of RP $^{5, 12}$. We also found statistically increased values of IgG index and de novo intrathecal IgG synthesis (Tourtelotte) in the group of patients with RP in comparison to the group of patients without RP. The acquired result indicates an increased immunologic activity within the CNS in MS patients with RP. These results are in accordance with the results in the literature $^{48, 50}$.

Within our research we determined the parameters of VEP. In the group of patients with RP, the low amplitude and prolonged latency were registered more commonly, in contrast to the group without RP. During the research, we paid attention to pathologically lowered amplitude, which indicated acute lesion, i.e. severe inflammatory reaction resulting in the lower amplitude and significant prolongation of latency in patients with RP. These results are in accordance with the results in the literature $^{1, 39, 51}$, although there are studies reporting differently. In our opinion, the differences in results are due to the selection of patients, since those studies included mainly outpatients with milder form of MS.

**Conclusion**

Our study suggests that the presentation of RP is more typical in MS patients with signs of blood-brain barrier impairment. In regard to this, RP might be considered a reliable indicator of MS activity. By monitoring RP presence and evolution, it might be possible to monitor the disease activity and treatment effects, without applying other, more expensive methods such as MRI.
REFERENCES


Received on December 16, 2009.
Accepted on March 26, 2010.