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Abstract.

Work objective: To study the relationship between the duration of remission after the onset, the severity of relapses against the background of different duration of the relapsing stage (RS) and the nature of the prognosis in the secondary progressive multiple sclerosis (SPMS) using clinical and mathematical analysis.

Material and research methods: Patients with different prognosis for SPMS; neurological examination using The Expanded Disability Status Scale (EDSS); a survey method. Mathematical methods: 'contingency tables 2x2’ (determining the significance of the connection between a pair of two indicators - different duration of remission after the onset and RS in four groups of patients), Yule's Coefficient of Association (determining the magnitude of differences between the group and the studied indicator), a permutation test (defining clinical indicators on RS, which significantly differed in mild and severe relapses).

Research results: Pairwise comparison in four groups of patients with different duration of remission after the onset and RS in SPMS showed that long-term remission after the onset and prolonged RS delay the transition of RS into secondary progression (SP). Short duration of these indicators revealed the opposite prognostic tendencies, indicating the further progression of the disease. The presence of severe relapses on RS in SPMS is predominantly associated with unfavorable prognostic indicators on RS and indicates the initiation of the transition into SP.

Conclusion: Accordingly, the duration of remission after the onset, the severity of relapses against the background of different durations of RS should be regarded as prognostic clinical markers that play a key role in the switch of RS to SPS in SPMS. The results obtained should be used to assess the current clinical situation and timely prescribe an appropriate pathogenetic therapy on RS.

Key words. Multiple sclerosis, secondary progressive course, prognosis, remission after the onset, severity of relapses, relapsing stage, Yule’s coefficient, contingency tables, permutation test.

Introduction.

Prognosticating in secondary progressive multiple sclerosis (SPMS) results from the interaction of various clinical indicators that characterize the disease course stages. Thus, a logical question arises whether the transformation of a recurrent course (RC) into a secondary progressive one is inevitable, or these are two different types of the course with different pathogenetic mechanisms of formation? [1-8].

Unlike RC, which is relatively stable and generally favorable in 10-15% of patients, SPMS is characterized by an accelerated accumulation of neurological deficit and an increase in the degree of disability with the formation of a final unfavorable prognosis in the vast majority of patients [1,9-13].

At the same time, some patients should be given a relatively “benign” prognosis as an indefinite one, which has characteristic features, the leading ones of which are a long relapsing stage (RS), slow progressive accumulation of neurological deficit during the secondary progression stage (SPS), an adequate response to various methods of pathogenetic and symptomatic therapy [10,13,14,15,16].

The paths along which the SPS is formed are of strategic importance for different prognosis options in SPMS. Repeat clinical analysis has shown that this stage forms and develops in two ways. Pathway 1 is more common and begins after a relapsing stage of varying duration; path 2 follows immediately after clinical remission after onset, bypassing RS. Therefore, the pathway 1 is regarded as more favorable due to the inclusion of such temporary stages of the disease as remission after the onset of various durations and RS, which temporarily prevent the formation and slow down the development of SPS. Pathway 2, which has no RS, is characterized by an accelerated formation of a persistent neurological deficit and a furthermore unfavorable course of the disease [10,14].

Long-term remission after the onset has been generally accepted to be an important criterion for the further benign course of the disease [17]. However, this statement, based on the clinical experience of previous generations of neurologists, is in conflict with recent studies, which, taking into account the introduction of neuroimaging research methods (MRI), indicate a continuous wave-like activity of the demyelinating process. Therefore, in the vast majority of patients, the so-called clinical remissions, which due to the MRI-revealed radiological activity proceed as pseudo-remissions, represent a stage in the subclinical course of MS. The longer this process proceeds, the more likely it causes depletion and disruption of adaptive-compensatory mechanisms due to the lack of adequate and timely pathogenetic therapy. This fact significantly increases the likelihood of further adverse courses of the disease in this category of patients [12,15,18,19].

The transformation of RC into SPMS requires a complex selective structural reorganization of various clinical indicators in RS (its duration, the rate of formation of neurological symptoms in different relapses, the severity and duration of relapses, the duration and completeness of clinical remissions between relapses, the dynamics and degree of accumulation of neurological deficit, according to the EDSS). The leading role...
among these indicators belongs to the duration of RS and the severity of relapses [10, 18, 19, 20].

With this in mind, the objective of this research was to study the relationship between the duration of remission after the onset, the severity of relapses against the background of different durations of RS, and the nature of the prognosis in SPMS using clinical and mathematical analysis.

One hundred patients with secondary-progressive stage (SPS) were examined. Eighty patients with relapsing stage (RS) were examined as a control group when analyzing the severity of recurrent course (RC). Therefore, in Table 5, "Significant differences between the frequency of clinical indicators in patients with severe and mild (and/or moderate) RS relapses in RC”, the number of patients with severe relapses (n=15), and mild relapses (n=65). A total of 80 patients.

Using the “2x2 contingency tables” (method of statistical analysis), the significance of the relationship between a pair of two indicators characterizing the clinical features of the course of remissions after the onset and RS according to the χ2 test was compared and assessed. The groups were distinguished taking into account the frequency of these indicators, for each of which non-random differences in their frequency were determined in the considered pairs of groups. The magnitude of the differences between the group and the studied indicator was assessed using the coefficient of colligation, which in this case was a correlation coefficient. With the help of a permutation test (method of statistical analysis) in SPMS and RC, clinical indicators were determined that significantly differed in RS in mild (and/or moderate) and severe relapses [10, 21-24].

Correlations between two indicators, the duration of remissions after the onset and the duration of RS, was compared in the following groups of SPMS patients:

- group 1 – short (and/or medium) remission after the onset and short (and/or medium) recurrent stage (46 people).
- group 2 – long remission after the onset and long recurrent stage (14 people).
- group 3 – short (and/or medium) remission after the onset and long recurrent stage (26 people).
- group 4 – long remission after the onset and short (and/or medium) recurrent stage (14 people).

Various prognosis outcomes were grouped as follows. Groups 1 and 4 had approximately the same distribution of prognosis outcomes that practically coincides with the distribution for all patients. While in group 2 the distribution of outcomes is “reverse”, with more common uncertain prognosis with the same proportion as in groups 1 and 4. In group 3, on the contrary, an unfavorable prognosis significantly prevails. All other cases, based on this table, show trends only (Table 1).

Considering these data using the contingency method, according to the χ2 test, we obtain a correlation between groups and percentages of the outcome of the final prognosis that is statistically significant (p<0.01). Since the differences in the duration of remission after the onset and the duration of RS in different groups are presented in various combinations, it can be assumed that these two factors are associated with the distribution of patients according to the nature of the prognosis in these four groups and that this distribution is not random.

To test this assumption, using the χ2 test, we assessed the relationship between the distribution of prognosis outcomes for the combined groups with one factor: groups with different duration of remission after the onset (1+3 and 2+4) and groups with different duration of RS (1+4 and 2+3). The first four-field table corresponds to the differences in the duration of remission after the onset (1+3) and includes all patients with short remissions after the onset and (2+4) with long remissions. The second four-field table corresponds to the differences in the duration of RS: (1+4) - short and (2+3) - long (Table 2).

Applying the χ2 test to two tables showed a weak correlation in the first case (1+3 and 2+4) and no correlation in the second (1+4 and 2+3). This indicates that only the combination of these two factors significantly predetermines the final outcome of the prognosis. Obviously, the outcome of the prognosis is also influenced by other signs that either themselves depend on the duration of remission and/or RS, or act independently. In order to identify "candidates" for this role, intergroup pairwise differences were analyzed.

Table 3 shows the clinical indicators, which correspond to a fairly large (0.7 or more) coefficient of colligation.

The absolute value of the coefficient of colligation (0.7 and more) indicates significant differences in its distribution between the studied groups. The (+) sign of the coefficient of colligation means that it is more common in group 1 of the compared pair, while (-) represents an alternative option.

It has been shown that long-term remission most often occurs after a mild (groups 1-2) or moderate (groups 2-3) onset, which is rapidly formed (groups 3-4). RS after long-term remission, in general, proceeds favorably and is characterized by mild (3-4 groups), short or medium-term relapses (2-4 groups), alternation of different rates of formation of clinical symptoms in relapses (2-4), long-term remissions between relapses (2-4 groups). Thus, long-term remission after the onset should be regarded as a favorable prognostic clinical marker for the further course of the disease.

Long-term RS, as well as post-onset long-term remission, is characterized by favorable prognostic indicators. These include

**Table 1. The nature of the prognosis and the duration of remissions after the onset and recurrent stage in 4 groups of patients with SPMS.**

<table>
<thead>
<tr>
<th>Group</th>
<th>Unfavorable prognosis (n=58)</th>
<th>Undefined prognosis (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (n=46)</td>
<td>56.5</td>
<td>43.5</td>
</tr>
<tr>
<td>Group 2 (n=14)</td>
<td>42.8</td>
<td>57.2</td>
</tr>
<tr>
<td>Group 3 (n=26)</td>
<td>69.2</td>
<td>30.8</td>
</tr>
<tr>
<td>Group 4 (n=14)</td>
<td>57.1</td>
<td>42.9</td>
</tr>
</tbody>
</table>

Note: n - number of patients

**Table 2. Prognosis for combined groups of SPMS patients with different duration of remissions after the onset and recurrent stage.**

<table>
<thead>
<tr>
<th>Group</th>
<th>Unfavorable prognosis</th>
<th>Undefined prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1+3</td>
<td>61</td>
<td>39</td>
</tr>
<tr>
<td>2+4</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>1+4</td>
<td>57</td>
<td>43</td>
</tr>
<tr>
<td>2+3</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>
mild and moderate onsets (groups 2-3), short relapses (groups 2-3), long-term remissions and alternation of remissions of different duration between relapses (groups 2-3). Despite the predominance of the final unfavorable prognosis, a longer RS improves the quality of life of these patients, postponing SPS. With a short and/or medium remission after the onset of RS, the course is ambiguous. A less aggressive course was observed in the subgroup of patients with remission after the medium onset. The structure of the RS was dominated by gradual formation of short and mild relapses (groups 1-2 and 1-3),

**Table 3.** Pairwise correlation (using contingency tables) between clinical indicators in 4 groups of SPMS patients.

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Coefficient of colligation (0.7 and more)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gradual symptom formation in RS relapses (groups 1 and 2)</td>
<td>+0.70</td>
</tr>
<tr>
<td>Alternation of different rates of symptom formation in relapses as the course progresses in RS (groups 1 and 2)</td>
<td>+1.0</td>
</tr>
<tr>
<td>Complete remissions between RS relapses (groups 1 and 2)</td>
<td>+0.77</td>
</tr>
<tr>
<td>Long remissions between RS relapses (groups 1 and 2)</td>
<td>+0.77</td>
</tr>
<tr>
<td>Alternation of remissions of different duration between RS relapses (groups 1 and 2)</td>
<td>+0.70</td>
</tr>
<tr>
<td>Short RS relapses (groups 1 and 3)</td>
<td>+0.70</td>
</tr>
<tr>
<td>Mild RS relapses (groups 1 and 3)</td>
<td>+0.79</td>
</tr>
<tr>
<td>Tendency to aggravation of RS relapses (groups 1 and 3)</td>
<td>+0.79</td>
</tr>
<tr>
<td>Tendency to aggravation of RS relapses (groups 1 and 3)</td>
<td>+0.75</td>
</tr>
<tr>
<td>Tendency to lengthening of RS relapses (groups 1 and 3)</td>
<td>+0.70</td>
</tr>
<tr>
<td>Long remissions between RS relapses (groups 1 and 3)</td>
<td>+0.87</td>
</tr>
<tr>
<td>Mild onset (groups 1 and 4)</td>
<td>-0.75</td>
</tr>
<tr>
<td>Short RS relapses (groups 1 and 4)</td>
<td>-0.73</td>
</tr>
<tr>
<td>Long RS relapses (groups 1 and 4)</td>
<td>+1.00</td>
</tr>
<tr>
<td>EDSS (groups 1 and 4)</td>
<td>-1.00</td>
</tr>
<tr>
<td>Moderate onset (groups 2 and 3)</td>
<td>+0.78</td>
</tr>
<tr>
<td>Alternation of different rates of symptom formation in RS relapses (groups 2 and 3)</td>
<td>-1.00</td>
</tr>
<tr>
<td>Mild onset (groups 2 and 4)</td>
<td>-0.72</td>
</tr>
<tr>
<td>Short RS relapses (groups 2 and 4)</td>
<td>-0.78</td>
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<tr>
<td>Medium RS relapses (groups 2 and 4)</td>
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<tr>
<td>Alternation of different rates of clinical symptom formation in RS relapses (groups 2 and 4)</td>
<td>-1.0</td>
</tr>
<tr>
<td>Long clinical remissions between RS relapses (groups 2 and 4)</td>
<td>-1.0</td>
</tr>
<tr>
<td>Alternation of clinical remissions of different duration between RS relapses (groups 2 and 4)</td>
<td>-0.72</td>
</tr>
<tr>
<td>Rapid formation of clinical signs of the onset (groups 3 and 4)</td>
<td>-0.72</td>
</tr>
<tr>
<td>Mild RS relapses (groups 3 and 4)</td>
<td>-0.81</td>
</tr>
<tr>
<td>Short RS relapses (groups 3 and 4)</td>
<td>-0.95</td>
</tr>
<tr>
<td>Long clinical remissions between RS relapses (groups 3 and 4)</td>
<td>-1.0</td>
</tr>
</tbody>
</table>

**Table 4.** Significant differences between the frequency of clinical indicators in patients with severe and mild (and/or moderate) RS relapses in SPMS.

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Patients with severe relapses (n=54)</th>
<th>Patients with mild (and/or moderate) relapses (n=46)</th>
</tr>
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<tbody>
<tr>
<td>RS relapse worsening</td>
<td>92.6±5.1</td>
<td>60.9±14.1</td>
</tr>
<tr>
<td>Long RS relapse</td>
<td>82.5±10.1</td>
<td>47.8±14.4</td>
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<tr>
<td>RS relapse lengthening</td>
<td>92.6±5.1</td>
<td>65.2±13.8</td>
</tr>
<tr>
<td>Alternation of different rates of formation of RS relapses</td>
<td>81.5±10.4</td>
<td>34.8±13.8</td>
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<tr>
<td>Short relapses between RS relapses</td>
<td>81.5±10.4</td>
<td>56.5±14.3</td>
</tr>
<tr>
<td>Moderate duration of remission after the onset</td>
<td>25.9±11.7</td>
<td>52.2±14.4</td>
</tr>
<tr>
<td>Short RS relapses</td>
<td>48.1±13.3</td>
<td>73.9±12.7</td>
</tr>
</tbody>
</table>

**Note:** n - number of patients

**Table 5.** Significant differences between the frequency of clinical indicators in patients with severe and mild (and/or moderate) RS relapses in RC.

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Patients with severe relapses (n=15)</th>
<th>Patients with mild (and/or moderate) relapses (n=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RS relapse worsening</td>
<td>60.0±24.8</td>
<td>16.9±9.1</td>
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<tr>
<td>RS relapse lengthening</td>
<td>60.0±24.8</td>
<td>20.3±9.7</td>
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<tr>
<td>Undefined prognosis</td>
<td>66.7±23.8</td>
<td>27.6±10.9</td>
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<tr>
<td>Moderate duration of remission after the onset</td>
<td>6.7±12.6</td>
<td>47.0±12.1</td>
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<tr>
<td>Mild RS relapses</td>
<td>40.2±24.8</td>
<td>86.4±8.3</td>
</tr>
<tr>
<td>Favorable prognosis</td>
<td>23.5±11.3</td>
<td>63.2±14.2</td>
</tr>
</tbody>
</table>

**Note:** n - number of patients

which alternated with complete and long remissions (groups 1-2 and 1-3). Subgroup 2 with a short remission after the onset has less favorable RS with a predominance of long-term relapses (groups 1-4) and their tendency to worsen and lengthen (groups 1-3 and 1-4).

In the case of short and/or medium RS opposite prognostic trends also prevailed. On the one hand, the subgroup of patients with medium RS more often had mild onsets (groups 1-4), short (1-3 and 1-4 groups) and mild (1-3) relapses, full-fledged (groups 1-2) and long-term (1-2 and 1-3) clinical remissions between relapses (1-2 groups). These indicated a more favorable course of the disease. On the other hand, the subgroup of patients with short RS more often had long-term relapses (groups 1-4) with their further lengthening and aggravation (groups 1-3). With such a structural configuration of indicators, conditions were created that contributed to the depletion of compensatory reserves, which led to an increased risk of SPS development.

The patients with mild (and/or moderate) and severe relapses were grouped based on the clinical characteristics of relapses of varying severity, which occurred in a different sequence during the course of RS and, as a rule, alternated with each other. Mild relapses were characterized by rapid formation of clinical symptoms, a short duration (no more than 3-4 weeks), mono- or oligosyndromic symptoms with minimal signs of
a rapidly regressing neurological deficit. Moderate relapses were characterized by oligo- or polysyndromic symptoms, predominantly developing at a gradual pace, the formation of a moderate neurological deficit with its further gradual regression over 2 or more months. In severe relapses, slow formation of severe polysyndromic clinical symptoms prevailed, followed by partial regression and gradual transformation (within 3 or more months) into short, unstable, and incomplete remissions [12,15,19,20].

Groups with mild (and/or moderate) relapses in SPMS showed a significant predominance of the average duration of remission after the onset and short RS relapses. Patients with severe RS relapses mostly had long-term relapses, alternation of different rates of relapse formation, worsening and lengthening of relapses, short remissions between relapses (Table 4).

The group of patients with a favorable prognosis in RC had no severe relapses accompanied by medium remission after the onset and mild relapses throughout the entire course of RS. In case of severe RS relapses, the uncertain prognosis prevailed, which was associated with such clinical indicators as worsening and lengthening of relapses (Table 5).

Thus, the study of comparative pairwise analysis of four groups of patients revealed complex and ambiguous correlations between different durations of prognostically important clinical indicators, i.e., clinical remission after the onset and RS in SPMS. It has been shown that long-term clinical remission after the onset plays a key role in the subsequent relatively benign course of SPMS. A prolonged RS for the final prognosis generally had a positive effect, postponing the transformation into SPMS. The greatest difficulty for assessing the prognosis was the interpretation of indicators that have short and medium remissions after the onset and a short and medium RS. For these indicators, directly opposite prognostic trends were found, indicating that medium remissions and medium RS turned out to be more favorable, and the short duration of these indicators was an unfavorable clinical marker of the further course of the disease.

The severity of RS relapses in SPMS and the MSRC should also be considered as a diagnostic indicator selectively associated with other clinical indicators that occur during clinical remission after the onset and in RS. For the group of patients with mild relapses in RS, the value of timely diagnosis of SPMS is not significant enough as it is close to the similar group of patients with RC. This circumstance can lead to an incorrect interpretation of the further course of the disease in this category of patients. Severe RS relapses in this type of course, on the contrary, may indicate the onset of transformation into SPS.

The presence of severe RS relapses in RC allows us to regard the further prognosis as uncertain, i.e., more unfavorable, and testify to the further possible formation of SPMS.

Thus, the duration of remission after the onset, the severity of relapses with different durations of RS should be regarded as prognostic clinical markers that play a key role in transforming RS to SPMS. The results of this study should be used to assess the current clinical situation and timely prescribe adequate pathogenetic therapy for RS.

REFERENCES