Multifactorial model of predictors of the development of depressive disorders in multiple sclerosis: a prospective longitudinal study

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Up to 50% of patients with multiple sclerosis (MS) are affected by depression.

Objective: *to develop a multifactorial model of predictors of depression in MS, considering sociodemographic, clinicopsychopathological and clinicofunctional characteristics.*

Material and methods. *157 patients with MS and depression were analyzed. The control group consisted of 100 MS patients without depression. The observation period was 10 years. The following scales were used: Beck, MFI-20, Spielberger-Hanin, visual analogue scale (VAS) for pain, PASAT test, EDSS. We performed an MRI scan, and identified significant stressful events, the type of MS, clinically isolated and radiologically isolated syndromes, concomitant diseases and the use of MS disease-modifying treatments (DMTs). The diagnosis of depression was made according to the ICD-10 criteria. Multivariate models were developed using analysis of variance and multiple linear regression equation.*

Results. *A multifactorial model of predictors for the development of depression with a high multiple correlation value (r=0.85) was proposed. Factors with pronounced influence on the development of depression were: high rate of progression of MS (Beta=0.879), highly active course of MS (Beta=0.876), asthenia 89.6±1.1 points on the MFI-20 scale with an increase of 1.48% per year (Beta=0.784). Significant factors were: localization of lesions in the frontal, temporal regions of the right hemisphere (Beta=0.742), reactive anxiety 56±2.64 points on the Spielberger-Khanin scale with an increase of 1.89 % per year (Beta=0.682), increase in the area of lesions in the brain by 1.83 % per year (Beta=0.618), multiple lesions in the brain (Beta=0.591). Statistically significant predictors with less influence on the development of depression were: female gender, secondary education, living alone, significant stressful events in the past, autoimmune diseases, depression before the development of MS, depression in close relatives, pain syndrome (6–8 points on VAS). Cognitive impairment, increase in PASAT score of 2.87% per year, body mass index with an increase of 1.61% per year, clinically isolated and radiologically isolated syndromes before the development of MS, age of onset of MS, age of onset of depression, disability indicator according to EDSS, type of MS, comorbidity and medication use are not predictors of depression in MS.*

Conclusion. *A high rate of MS progression, a very active course of MS, an increase in asthenia on the MFI-20 scale, localization of lesions in the frontal and temporal regions of the right hemisphere and an increase in reactive anxiety were identified as important predictors of depression in MS.*

Keywords: *multiple sclerosis; depressive disorders; predictors.*

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Depression is the most common mental disorder in multiple sclerosis (MS). According to the previous studies, up to 50% of patients with MS suffer from depression [1]. The onset of depression can lead to a decrease in the quality of life and is often accompanied by suicidal thoughts or behavior, non-compliance to treatment, loss of physical abilities and a more severe course of MS [2–6].

While the use of pathogenetic therapy (modulators and suppressors of the immune system) increases, the course of MS tends to become more aggressive. Therefore, the study of predictors of depression in MS has become important due to its high prevalence and social significance. Thus, creating new prognostic and diagnostic approaches has become crucial [7,8].

According to the analysis of cross-sectional studies, depression in MS may be associated with uncertain outcome of the disease, its impact on everyday life, loss of hope, stress and, finally, with the characteristics of coping mechanisms. Moreover, physical and cognitive impairment, as well as β-interferon therapy and immune dysfunction can also be significant risk factors for the onset of depression [9].

However, the evidence base for the predictors of affective disorders identified in cross-sectional studies is limited, as only few longitudinal studies on the risk factors of depression in MS have been conducted.

Recent studies suggest that young people with fatigue and sleep disorders are more likely to develop depression, the average time between MS onset and diagnosis being 3.5 years.

Notably, the presence of pain and decreased physical activity at the beginning of the study were not regarded as predictors of depression [10]. According to S. Simpson Jr et al. [11], there was an association between positive screening for depression and the secondary progressive course of MS, fatigue and presence of co-morbidities. Additionally, negative screening for depression was correlated with high socioeconomic status and being in a relationship. K.L. Taylor et al. [12] found a lower risk of depression in patients who consumed moderate amounts of alcohol (less than 30 grams per day for women and 45 grams per day for men) and took vitamin D and omega-3 supplements.

In longitudinal studies the significance of rapid progression of MS, highly active course of MS, the presence of clinically and radiologically isolated syndromes and active lesions on MRI were not previously investigated as possible predictors of depression development.

The aim of the study is to propose a multifactorial model of predictors of depression in MS, taking into the account sociodemographic, psychopathological and radiological characteristics.

Materials and methods. The longitudinal prospective study was conducted. The examination scheme was partially described in the previous publication [13]. Some characteristics were measured at the time when MS diagnosis was established, others (such as area of brain demyelination, reactive anxiety on Spilberger-Hanin scale, asthenia on MFI-20 scale, rate of MS progression according to EDSS, cognitive impairment according to PASAT, and BMI) were measured in dynamics: at the time of MS diagnosis and at least once a year over the 10-year period of follow-up. All patients were consulted by a psychiatrist to determine whether they had any mental disorder. The second interview was conducted 6 months after the first one, and then patients were examined by a psychiatrist at least once a year over the 10-year period of follow-up. All the examinations were done on an outpatient basis after getting a local ethical committee approvement. Thirteen patients dropped out of the study and were excluded from the database.

After the exclusion of dropouts, the database consisted of 750 patients with MS, who lived in Ivanovo and Ivanovo region. All of them were regularly examined by a psychiatrist. 300 patients were diagnosed with a mental disorder, and depression was found in 157 out of 300 cases (52.3%). Patients with depression were included in the main observation group; the control group consisted of 100 patients of comparable age and sex, but without depression episodes. The control group was randomly selected from 593 patients without mental disorders included in the database. The average time from MS diagnosis to diagnosing depression was 4.5±2.5 years.

Clinical manifestations of depression appeared to be typical, atypical or masked. The typical one was vital depression, which was identified in 117 (74.52%) patients. Atypical depressive features (without classical depressive triad) were found in 37 (23.57%) patients, including 11 (7.01%) patients with apathetic depression, 9 patients (5.73%) with asthenic depression and 17 (10.83%) with anxious depression. Finally, 3 patients (1.91%) were diagnosed with masked depression.

MS was diagnosed by a neurologist according to McDonald (2017) criteria [14]. The criteria for highly active MS (HAMS) were as follows: 2 or more exacerbations per year, appearance of one or more active lesions within a year (detected using contrast-enhanced T1-weighted imaging), and/or two or more new lesions on T2-weighted imaging, an increase in the size of existing lesions based on magnetic resonance imaging (MRI) with contrast gadolinium enhancement (conclusions regarding MRI findings were made by an independent expert who performed the MRI study) and an increase by 1–1.5 points per year on the Kurtzke Expanded Disability Status Scale (EDSS) determined by a neurologist.

In the main group most patients were single (56.69%), had secondary education (43.31%), had no job (59.24%), experienced stressful events before MS manifestation (31.21%) and had a family history of depression (33.1%).

In the control group fewer patients were single (5.0%), patients less often had secondary education (10.0%), less frequently did not work or study (11.0%) or experienced significant stressful events (SSE) before MS manifestation (2.0%).

The disease course in the main group was as follows: remitting MS (RMS) – 90 (57.3%) patients, including HAMS – 15 (16.7%) patients; secondary progressive MS (SPMS) – 55 (35.0%) patients; primary progressive MS (PPMS) – 12 (7.6%) patients. In the control group the disease course was characterized as: RMS – 65 (65.0%) patients, including 4 (6.2%) people with HAMS; SPMS – 25 (25.0%) patients, PPMS – 10 (10.0%) patients. 48 (30.57%) and 31 (19.75%) patients from the main group met the criteria for clinically isolated syndrome (CIS) and radiologically isolated syndrome (RIS), respectively, before MS manifestation. In the control group CIS was identified in 2 (2.0%) patients and RIS was not found.

The severity of depressive symptoms was measured using Beck's scale: mild degree (10–15 points) was identified in 57 (36.31%) patients, moderate degree (16-19 points) – in 76 patients (48.41%), severe degree (20–29 points) – in 24 (15.29%) patients out of the total number (157).

All patients at the time of inclusion in the study were taking medications for managing MS, including MS modifying therapies (MSMT); in the main group: glatiramer acetate – 27.0%, interferon-β – 55.41%, teriflunomide – 17.2%; in the control group: glatiramer acetate – 27.05%, interferon-β – 56.0%, teriflunomide – 17.0%.

Exacerbations of MS against the background of MSMT occurred rarely: in 29.94% of patients in the main group and in 27.0% of cases in the control group, and did not affect the development of depression. In HAMS exacerbations occurred at least twice a year.

Concomitant autoimmune diseases (thyroid gland pathology) were identified in 69.43% of patients from the main group and in 20.0% of patients from the control group. Depression was diagnosed according to ICD-10 depressive episode criteria, and Beck's scale was used to evaluate its severity. The list of significant stressful events was prepared using Holmes–Rahe Stress Inventory regardless of the weight of these events. Intensity of pain was evaluated with Visual Analogue Scale (VAS), MFI-20 was used to assess asthenia. Studies of personal and reactive anxiety were conducted using the Spielberger–Hanin anxiety scale. PASAT was used to measure cognitive impairment. MRI protocol included the following technical characteristics: Siemens MAGNETOM AVANTO MRI system with a magnetic field strength of 1.5 Tesla; T2, T1, 3D FLAIR, WI images in coronal, sagittal, and

axial planes with contrast enhancement. The localization of the brain lesions was determined by identifying hyperintense areas on T2-weighted and FLAIR images. MRI scans were performed on patients according to a standardized protocol. If 20 or more hyperintense lesions were identified, they were considered to be multiple lesions. The data were interpreted by a neurologist. Then the rate of disease progression (RP) was calculated as the ratio of the EDSS score (points) to MS duration (years). According to the data obtained, 3 types of MS progression were identified: slow - less than 0.3 points per year on EDSS, moderate – 0.3–0.74 EDSS points per year, and fast – more than 0.74 points per year. Functional impairment of the central nervous system was assessed using EDSS (from 0 to 10 points).

The statistical analysis was conducted using Statistica 6.0 software. Using variance analysis, an initial selection of risk factors was made. These factors demonstrated a correlation with the development of depressive symptoms in MS patients. To construct a multifactorial model, mathematical method of multiple linear regression equations was used. Using a multifactorial variance analysis, the relationship between the probability of developing depression in different MS subtypes and certain predictors was determined, while factors that were not significantly associated with depression were removed from the list. Some predictors were dynamic, such as reactive anxiety on the Spielberger–Khanin scale, asthenia on the MFI-20 scale, increased area of demyelination foci in the brain over time according to MRI findings, cognitive impairment assessed by the PASAT test, and body BMI (excessive weight). Other predictors were recorded at the time of the diagnosis of MS.

Results. Based on the analysis of socio-demographical, psychopathological and radiological characteristics, using multiple regressive analysis, the final list of factors that may predict depression in MS, was established. Initially, the following additional risk factors were considered potential predictors of depression: the age at which MS was diagnosed, the age of depression manifestation, the EDSS disability score, the type of MS, and the use of medications that may influence the risk of depression in MS (MSMT, corticosteroids, and anticholinergics). However, after statistical analysis, these factors did not demonstrate a significant association with the onset of depression and were therefore excluded from further consideration.

During the next step, the quantitative values of the contribution of predictors to the development of depressive disorders were determined. After the model was developed, the coefficient of determination R^2 was calculated, which was 0.31 for this model. This demonstrated the average degree of variation in the values of the dependent variable for different combinations of independent variables included in the model. As a result of the analysis, the p-value (p=0.0000001) for this multiple regression equation was found to be less than 0.05. This indicates that the proposed model accurately reflects the relationship between the included characteristics. The standard error of model estimation (25.65) indicates an acceptable level

Table 1. *Predictors of the development of depression in MS*

Predictors	SS	df	MS	F	p
Interval	260.415	1	260.415	1073.745	0
Sex (female)	0.537	1	0.537	1.322	0.104
Education (secondary)	0.111	1	0.111	0.421	0.301
Living alone	0.761	2	0.457	1.025	0.105
Not working	0.989	1	0.863	2.964	0.036
Significant stressful events	0.937	1	0.927	2.944	0.026
Presence of depression in close relatives	1.654	2	0.749	3.244	0.041
Depression prior to MS manifestation	1.972	2	0.848	3.746	0.031
History of autoimmune diseases	0.554	2	0.543	1.205	0.051
Multiple lesions on MRI	1.419	2	0.937	3.781	0.0242
Localization of lesions mainly in the frontal and temporal lobes of the right hemisphere	1.714	2	0.799	3.343	0.041
Highly active MS (HAMS)	1.978	2	0.845	4.264	0.042
History of clinically isolated syndrome (CIS)	1.422	2	0.479	2.244	0.043
History of radiologically isolated syndrome (RIS)	1.352	2	0.344	2.234	0.021
Dynamical predictors					
Increase in the area of brain demyelination lesions by 1.83% per year	2.307	3	0.634	2.988	0.0301
Reactive anxiety 56±2.64 points on the Spielberger State-Trait Anxiety Inventory (STAI) adapted by Khanin with an increase by 1.89% per year	1.943	2	0.949	3.949	0.052
Asthenia level 89.6±1.1 points on the MFI-20 scale with an increase by 1.48% per year	1.342	2	0.636	4.834	0.027
High rate of MS progression (0.74 points per year) on EDSS with N. Malkova adaptation	1.981	2	0.799	3.347	0.047
An increase in cognitive impairment measured using PASAT by 2.87% per year	1.969	2	0.949	3.346	0.041
High BMI with an increase by 1.61% per year	1.110	3	0.838	1.781	0.050

Note. SS – the sum of the squared differences between the sample means and actual values for each type of variation; df – the number of freedom degrees for each type of variance; MS – the mean sum of squared differences for each type of variance, defined as SS/df; F – value of Fisher's statistics for MS; p – the significance level for F value.

of variability between actual and predicted values for the selected predictors and the dependent variable. The results are summarized in Table 1.

The next step consisted in identifying weighted coefficients (Beta) for each of the independent characteristics. The higher Beta was, the more significant was the influence of the predictor on depression manifestation. The results are summarized in Table 2.

The discriminant functional analysis identified a high level of multiple correlation (r = 0.85).

Thus, the predictors with significant influence on the development of depression, according to regression equation, were: high rate of MS progression (0.74 points on EDSS per year) (Beta = 0.879), HAMS (Beta = 0.876), asthenia level 89.6±1.1 points on MFI-20 with an increase by 1.48% per year (Beta = 0.784).

The following factors also turned out to be significant: the localization of demyelination lesions mainly in the frontal and temporal lobes of the right hemisphere, reactive anxiety score 56±2.64 points measured by Spielberger–Hanin scale with an increase by 1.89% per year (Beta = 0,682), an increase in the area of brain lesions by 1.83% per year (Beta = 0,618) and presence of multiple demyelination foci in the brain (Beta = 0,591).

Such factors as female sex, secondary education, having no family, experiencing significant stressful events, having other autoimmune disorders or depression prior to MS manifestation ($p < 0.05$, $r = 0.388$), high level of pain (6–8 points on VAS), cognitive impairment, increase in the PASAT score by 2.87% per year, high BMI (excessive body mass) with an increase by 1.61% per year appeared to be statistically significant, but had less influence on the development of a depressive disorder. Clinically and radiologically isolated syndromes were also identified as predictors of depression.

Therefore, the proposed multifactorial model helps to develop a personalized approach to providing specialized medical care for patients with MS based on the prognosis of depression development.

Discussion. Using the database of 750 patients with MS, we found 300 patients with mental disorders, of whom 157 suffered from depressive disorders, which accounted for 29.9% of the total number of patients. Since the clinical approach to identifying depression was used, the percentage of cases in which depression was diagnosed, is lower than in other studies in which depression was identified using psychometric inventories.

In our study the age of patients was not found to be a significant predictor of the development of depression. S. Simpson Jr et al. [11 did not establish a predicative value of the age either. However, in the prospective cohort study, K.A. Edwards et al. found that younger age can be a risk factor for depression development [10].

The obtained data about the female sex as a predictor of depression contradict

Table 2. *Quantitative values of the predictors for the development of depressive disorders in MS*

Predictors	Beta	Std. Err.	B	Std. Err.	t	p-level
Intercept (a constant)	–	–	24.619	5.983	-4.127	0.00004
Sex (female)	0.261	0.031	0.362	0.055	4.140	0.00000
Education (secondary)	0.174	0.034	0.374	0.056	4.241	0.00000
Living alone	0.084	0.038	0.184	0.095	3.393	0.00001
Not working	0.068	0.032	-1.187	0.481	-2.61	0.00812
Significant stressful events	0.078	0.082	0.048	0.028	6.182	0.00001
Presence of depression in close relatives	0.099	0.089	0.096	0.029	6.889	0.00003
Depression prior to MS manifestation	0.148	0.048	1.387	0.451	6.548	0.00033
History of autoimmune diseases	0.591	0.038	0.834	1.854	9.140	0.00000
Multiple lesions on MRI	0.048	0.022	0.162	0.072	1.464	0.02001
Localization of lesions mainly in the frontal and temporal lobes of the right hemisphere	0.742	0.048	0.729	1.138	6.168	0.00000
Highly active MS (HAMS)	0.876	0.068	2.463	1.458	9.981	0.00000
History of clinically isolated syndrome (CIS)	0.181	0.062	0.319	0.724	3.462	0.00021
History of radiologically isolated syndrome (RIS)	0.172	0.044	0.377	0.671	3.341	0.00011
Dynamical predictors						
Increase in the area of brain demyelination lesions by 1.83% per year	0.682	0.058	0.680	1.178	7.174	0.00262
Reactive anxiety 56±2.64 points on the Spielberger State-Trait Anxiety Inventory (STAI) adapted by Khanin with an increase by 1.89% per year	0.784	0.068	0.687	1.244	6.271	0.00000
Asthenia level 89.6±1.1 points on the MFI-20 scale with an increase by 1.48% per year	0.618	0.089	0.686	1.243	7.183	0.00000
High rate of MS progression (0.74 points per year) on EDSS with N. Malkova adaptation	0.879	0.069	3.982	1.348	9.713	0.00000
Increase in cognitive impairment measured using PASAT by 2.87% per year	0.183	0.089	0.699	1.744	7.291	0.00002

Note. Beta is a standardized coefficient, B is a non-standardized coefficient, Std. Err – standard error, t – t-criterion

the results of the previous studies [11, 12] in which sex was not shown to be a reliable predictor of depressive disorders.

Our study has shown that the risk of depression development is associated with such social factors as low level of education, having no job and living alone. S. Simpson Jr et al. [11] came to the same conclusions, but demonstrated a higher influence of living alone on depression development than in our study.

We found that a high BMI with an increase of 1.61% per year can be a risk factor for depression. This dynamic indicator, however, showed a weak relationship within the framework of the analysis of variance. Indirectly, this coincides with the previously established prognostic association of BMI with the risk of depression in patients with MS [11]. The association of the risk of depression in MS is explained by the inflammatory basis of obesity [16].

The authors of a number of longitudinal studies pointed to the significant predictive value of asthenia score in assessing the risk of depression [11, 12]. Based on a multifactorial model, we have established for the first time that not only the initial level of asthenia is important, but also its increase by 1.48% per year (Beta=0.784).

According to S. Simpson Jr et al. [11], the disability index (estimated on the PDDS scale) is a significant predictor of the development of depression, which was not confirmed in our study. At the same time, our data on the absence of the impact of disability on the likelihood of depression coincides with the results obtained by Edwards [10], who measured disability using EDSS. The reason for this difference may be the method of disability assessment. We evaluated the indicator using the Kurtzke scale (EDSS). The interchangeability of these scales (PDSS and EDSS), especially in patients with mild and moderate MS, remains questionable [17].

An association between the type of MS course and the risk of depression was not found either, in contrast to the previously demonstrated association of depression development with the secondary progressive type of MS course [11]. Our findings regarding the absence of an association between the type of MS and the likelihood of developing depression in patients are consistent with the results of a meta-analysis conducted by D.S. Peres and colleagues, which included both cross-sectional and longitudinal studies. The meta-analysis found a similar strength of association between depression and both progressive multiple sclerosis (PMS) and relapsing-remitting multiple sclerosis (RRMS) [18].

The progression of cognitive impairment in MS patients with depression was reported by some researchers [19, 20]. As part of a longitudinal study, we have for the first time established an increase in cognitive impairment on the PASAT scale by 2.87% per year as a risk factor for depression.

We have not established the relationship between the development of depression and the use of MSMT which coincides with the data obtained by Simpson Jr et al [11].

Conclusion. In this longitudinal study we for the first time established a number of predictors of the development of depressive disorders: a high rate of progression of MS (0.74 EDSS points per year) (Beta=0.879), a highly active course of multiple sclerosis (HAMS) (Beta=0.876), clinically isolated syndrome (CIS) in the anamnesis, radiologically isolated syndrome (RIS) in the anamnesis, multiple lesions on MRI, an increase in the area of existing foci by 1.83% per year, localization of foci mainly in the frontal and temporal lobes of the right hemisphere.

Our findings regarding the association between EDSS dynamics and the likelihood of depression development indirectly contradict the conclusions of a meta-analysis of mixed (cross-sectional and longitudinal) studies conducted by D.S. Peres et al suggesting that there is no association between the EDSS score and the prevalence of depression.

The developed model can be used for personalized prediction of the development of depression in MS patients.

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