8. Madziyire MG, Magwali TL, Chikwasha V, Mhlanga T. The causes of infertility in women presenting to gynaecology clinics in Harare, Zimbabwe; a cross sectional study. Fertil Res Pract. 2021 Jan 5;7(1):1. doi: 10.1186/s40738-020-00093-0.
9. Mascarenhas MN, Flaxman SR, Boerma T, Vanderpoel S, Stevens GA. National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. PLoS Med. 2012;9(12): e1001356. doi: 10.1371/journal.pmed.1001356.
10. McGeachy MJ, Cua DJ, Gaffen SL. The IL-17 Family of Cytokines in Health and Disease. Immunity. 2019 Apr 16;50(4):892-906. doi: 10.1016/j.immuni.2019.03.021.
11. Sanderman EA, Willis SK, Wise LA. Female dietary patterns and outcomes of in vitro fertilization (IVF): a systematic literature review. Nutr J. 2022 Jan 18; 21(1):5. doi: 10.1186/s12937-021-00757-7.
12. Sequeira K, Espejel-Núñez A, Vega-Hernández E, Molina-Hernández A, Grether-González P. An increase in IL-1β concentrations in embryo culture-conditioned media obtained by in vitro fertilization on day 3 is related to successful implantation. J Assist Reprod Genet. 2015 Nov;32(11):1623-7. doi: 10.1007/s10815-015-0573-4.
13. Stojanovic Gavrilovic AZ, Cekovic JM, Parandilovic AZ, Nikolov AB, Sazdanovic PS, Velickovic AM, et al. IL-6 of follicular fluid and outcome of in vitro fertilization. Medicine (Baltimore). 2022 Jul 22;101(29): e29624. doi: 10.1097/MD.0000000000029624
14. WHO. Infertility is a global public health issue. WHO. World Health Organization; [cited 2020 May 31]. Available from: http://www.who.int/reproductivehealth/topics/infertility/perspective/en/
15. Zhang Y, Wang Y, Li MQ, Duan J, Fan DX, Jin LP. IL-25 promotes Th2 bias by upregulating IL-4 and IL-10 expression of decidual γδT cells in early pregnancy. Exp Ther Med. 2018 Feb;15(2):1855–1862. doi: 10.3892/etm.2017.5638.

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PROGNOSIS OF DISABILITY IN RELAPSING-REMITTING MULTIPLE SCLEROSIS

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105 patients with relapsing-remitting multiple sclerosis aged 18 to 49 were examined. The degree of disability was assessed using the Expanded Disability Status Scale. Neuropsychological examination was performed to determine the level of personal and reactive anxiety on the Spielberger-Khanin scale and depression on the Beck scale. Magnetic resonance imaging of the brain was performed and brain atrophy indices were calculated, namely, the bicaudal and Sylvian sulcus indices. The ability of the studied clinical and paraclinical indicators to predict the progression of disability in multiple sclerosis was assessed using ROC analysis. Areas under the ROC curve had excellent prognostic characteristics for indices of atrophy, levels of anxiety and depression about significant neurological manifestations (EDSS≥3.5 points) and disability in patients with relapsing-remitting multiple sclerosis. According to the data of the multiple logistic regression analysis, it was established that the degree of subcortical atrophy according to the BCR index is a statistically significant independent factor affecting the appearance of significant neurological manifestations, according to the adjusted odds ratio, purified from the influence of other factors (OR=26.2; 95 % CI 3.5–198.3), the level of depression on the BDI scale (OR=97.2; 95 % CI (3.4–2744.0). A significant protective effect of disease-modifying therapy was confirmed (OR=0.006; 95 % CI 0.001–0.045).

Key words: multiple sclerosis, atrophy, disability, prognosis, course.

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ПРОГНОЗУВАННЯ ІНВАЛІДИЗАЦІЇ ПРИ РЕЦИДИВУЮЧЕ-РЕМІТУЮЧОМУ РОЗСІЯНОМУ СКЛЕРОЗІ

Обстежено 105 хворих на рецидивуюче-ремітуючий розсіяний склероз у віці від 18 до 49 років. Ступінь інвалідизації оцінювали за шкалою Expanded Disability Status Scale. Проводили нейропсихологічне обстеження з визначенням рівня особистісної та реактивної тривожності за шкалою Спілбергера-Ханіна та рівня депресії за шкалою Бека. Проводили магнітно-резонансну томографію мозку та розраховували індекси атрофії мозку, а саме – бікаудальний та індекс Сильвієвої борозни. Здатність вивчених клінічних та параклінічних показників прогнозувати прогресування інвалідизації при розсіяному склерозі оцінювали за допомогою ROC-аналізу. Площі під ROC-кривою мали відмінні прогностичні характеристики для індексів атрофії, рівнів тривожності та депресії щодо значних неврологічних проявів (EDSS≥3.5 балів) й інвалідизації у хворих на РРРС. За даними множинного логістичного регресійного аналізу встановлено, що статистично значущими самостійними факторами впливу на появу значних неврологічних проявів, згідно скоригованих, очищених від впливу інших чинників, відношення шансів є ступінь підкоркової атрофії за індексом BCR (ВШ=26.2; 95 % ДІ 3.5–198.3), рівень депресії за шкалою BDI (ВШ=97.2; 95 % ДІ (3.4–2744.0). Підтверджено значний захисний ефект прийому хворобо-модифікуючої терапії (ВШ=0.006; 95 % ДІ 0.001–0.045).

Ключові слова: розсіяний склероз, атрофія, інвалідизація, прогнозування, перебіг.

The study is a fragment of the research project "Clinical, pathogenetic and prognostic markers of disorders of the nervous system and optimization of diagnostic and treatment algorithms", state registration No. 0122U201970.

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS) in which inflammation and demyelinating disease occur even in the early stages of the disease [3].

There are 4 types of MS course: relapsing-remitting (RRMS), secondary progressive, primary progressive and progressive-relapsing. RRMS is the most common one [6].

The incidence and prevalence of MS varies widely around the world. Geographical factors and different diagnostic and treatment options in individual countries influence this. The prevalence of MS has been steadily increasing over the past decade and averages 35.9 cases per 100,000 population. According to estimates, about 2.8 million people worldwide suffer from MS. The average age of diagnosis is 32 years [6, 11].

The course of the disease can vary significantly in patients. Although significant advances in treatment have been achieved in recent years due to a fairly wide selection of drugs for disease-modifying therapy (DMT), multiple sclerosis remains one of the most frequent causes of neurological disability at a young age [5, 10].

The possibility of predicting the onset or progression of disability in patients with MS remains open [1]. Although certain factors of the severe course of MS are currently known (number of exacerbations, localization of foci of demyelination), it is relevant to create a prognostic model of the course of MS taking into account the data of clinical, neuropsychological, and neuroimaging examinations and their comparisons.

The purpose of the study was to establish the prognostic value of clinical, morphometric and neuropsychological factors of the severe course of the disease and to develop a prognostic model for the progression of neurological deficits and disability.

Material and methods. 105 patients with RRMS aged 18 to 49 were examined, including 74 women (70.5 %) and 31 men (29.5 %). The ratio of women to men in the studied sample was 2.4:1 in general, which generally reflects the epidemiological features of the disease.

The clinical and neurological examination included the collection of complaints, disease and life history, and neurological examination with the Expanded Disability Status Scale (EDSS) score. The level of anxiety was assessed according to the Spielberger-Khanin scale, and depression – according to the Beck Depression Inventory (BDI). Patients underwent an MRI of the brain to determine cortical (SFR index – Sylvian Fissure Ratio) and subcortical (BCR – Bicaudal Ratio index) atrophy indices. Assessment of DMT was carried out.

The results of the study were processed using a personal computer using Microsoft Excel software products (Microsoft Office 2016 Professional Plus, Open License 67528927), STATISTICA 6.1 (StatSoftInc., serial number AGAR909E415822FA) and MedCalc Statistical software trial version 20.305 (MedCalc Software, Belgium; https://www.medcalc.org; 2022). Methods of descriptive and analytical biostatistics and multivariate statistical analysis were used.

Parametric characteristics and analysis methods were used under the normal distribution law. Non-parametric characteristics and criteria were used for data whose distribution differed from normal.

Correlation analysis was carried out by calculating Spearman's rank correlation coefficients (r_s), simple paired and multiple logistic regression analysis, and the odds ratio (OR) calculation. ROC analysis (ROC – Receiver Operating Characteristic curve analysis) was performed to determine the discriminating ability of the parameters. The critical value of the level of statistical significance (p) for all types of analysis was taken to be <5 % ($p<0.05$).

Results of the study and their discussion. The distribution of the studied sample of patients according to the EDSS scale showed that the largest share among the examined had a score of 2: among women – 27 %, among men – 22.6 %, in general –25.7 %. The largest share of patients – 85 people (81 %) had scores on the EDSS scale of 1.5–3.5 points without statistically significant differences by gender ($p=0.699$). At the same time, the highest score of 5.5 points was observed only in one woman.

Therefore, the sample of subjects included many people with the initial stages of MS, which are associated with minor limitations of the ability to work in everyday life and physical activity. This made it possible to analyze the progression of neurological deficits in patients with RRMS. Given that the degree of disability on the EDSS scale ≤3.5 points is defined as mild, and most patients had this level of disability, they were divided into group 1, patients with 3.5 to 6.5 points – into group 2 (moderate degree of disability). The appropriateness of this distribution was confirmed using cluster analysis.

The distribution of patients by study groups and the general characteristics of the examined patients are given in Table. 1.

The average level of depression, determined on the Beck scale, was 16.0 (13.0; 18.0) points among all the examined. In patients of the 1st group – 14.0 (11.0; 16.0) points, while in patients of the 2nd group, it was significantly higher ($p<0.001$) and was 19.0 (19.0; 24.5) points.

The assessment of the level of anxiety according to the Spielberger-Khanin scale showed that in most patients (84.8 %), the level of reactive anxiety (RA) was moderate (31–44 points) and on average was 36.0 (34.0; 39.0) points. Personal anxiety (PA) indicators in most cases (69.5 %) were low (up to 30 points)

and averaged 27.0 (24.0; 31.0) points. It should be noted that the level of situational anxiety exceeded the level of personal anxiety in the study groups and in general among all the examined (*p<0.001* in all comparisons), which is characteristic of neurological patients.

Table 1

General characteristics of the examined patients

Characteristics	All examined	Group 1	Group 2	*p*
Total number, n (%)	105 (100)	73 (69.5)	32 (30.5)	-
Gender, n (%)				
Women	74 (70.5)	49 (67.1)	25 (78.1)	*0.255*
Men	31 (29.5)	24 (32.9)	7 (21.9)	
Age distribution, n (%)				
up to 25 years old	15 (14.3)	10 (13.7)	5 (15.6)	*0.267*
from 25 to 30 years old	25 (23.8)	21 (28.8)	4 (12.4)	
from 30 to 35 years old	30 (28.6)	20 (27.4)	10 (31.3)	
from 35 to 40 years old	21 (20)	15 (20.5)	6 (18.8)	
40 years and older	14 (13.3)	7 (9.6)	7 (21.9)	
Age characteristics, M (SD).				
Average age, years	31.9 (6.95)	31.5 (6.7)	32.9 (7.53)	*0.225*
DMT				
did not receive	58 (55.2)	26 (35.6)	32 (100)	*<0.001*
received	47 (44.8)	47 (64.4)	0 (0)	

Note. *p* – differences between groups according to Pearson's χ^2 for qualitative signs, according to Student's t-test for quantitative characteristics

Determination of morphometric indices of subcortical and cortical atrophy of the brain showed the predominance of subcortical atrophy over cortical atrophy (*p<0.001*) in the study groups and in general among all the examined.

According to the studied brain atrophy indices, statistically significant differences were identified between the study groups with statistically significantly higher (*p<0.001*) average indicators in patients of the 2nd group compared to the 1st: according to the BCR index – 0.146 (0.145; 0.148) vs 0.139 (0.138; 0.141); according to the SFR index – 0.051 (0.046; 0.055) vs 0.037 (0.035; 0.040).

When developing a prognostic model of the progression of disability in RRMS, which was carried out based on a comparative analysis of the results and the conducted correlation analysis, factors that had high correlation coefficients with the EDSS disability scale were selected, in particular: depression scores on the Beck scale (r_s=0.98; *p<0.001*), the degree of RA and PA on the Spielberg-Khanin scale (respectively r_s=0.98; *p<0.001* and r_s=0.81; *p<0.001*), BCR and SFR indices (respectively r_s=0.84; *p<0.001* and r_s=0.81; *p<0.001*), reception of DMT (r_s=-0.79; *p<0.001*).

Areas under the ROC curve had excellent characteristics for indices of atrophy, levels of anxiety and depression, and for taking DMT –good characteristics of predictive ability regarding the development of significant neurological manifestations (EDSS≥3.5 points) in patients with RRMS (Table 2).

Table 2

Operational characteristics of indices of clinical, neuroimaging and neuropsychological examination of patients with RRMS regarding the prediction of significant neurological manifestations

Parameters	AUC	SE AUC	95 % CI AUC	*p*	Se	Sp	Optimal cut-off point
Absence of DMT 1 – yes, 0 – no)	0.822	0.028	0.735–0.890	*<0.001*	100.0	74.4	>0
BCR index	0.921	0.031	0.852–0.965	*<0.001*	96.9	75.3	>0.141
SFR index	0.924	0.035	0.855–0.966	*<0.001*	90.6	91.8	>0.043
PA level, points	0.908	0.024	0.874–0.976	*<0.001*	84.3	83.2	>30
RA level, points	0.918	0.002	0.962–1.000	*<0.001*	86.9	90.0	>38
BDI score, points	0.917	0.006	0.945–1.000	*<0.001*	89.1	85.9	>17

Notes. AUC (area Under Curve) – area under the ROC curve; SE (Standard Error) – standard error; Se (Sensitivity) – Sensitivity; SP (Specificity) – specificity; Optimal cut-off point – optimal cut-off point

The chances of developing significant neurological manifestations (EDSS≥3.5 points) in patients with RRMS increase by 94.7 times when the BCR index>0.141 increases (95 % CI 12.1–744.1; *p<0.001*);

index SFR>0.043 in 107.9 times (95 % CI 25.2–461.5; *p<0.001*); in the absence of CMT by 116.5 times (95 % CI 6.9–1980.7; *p<0.001*).

A PA level of more than 30 points increases the chances of having a clinically significant neurological deficit (EDSS≥3.5 points) by 73.4 times (95 % CI 19.7–274.2; *p<0.001*), a depression level of more than 17 points on the Beck scale – by 421.6 times (95 % CI 47.2–3762.18; *p<0.001*).

To assess the probability of developing significant neurological manifestations and disability in patients with RRMS (EDSS score≥3.5 points), multiple logistic regression analysis was performed with indicators that can potentially be used as predictors determined by preliminary correlation and ROC analysis and OR assessment. PA and depression levels, BCR and SFR indices, and DMT intake were considered potential predictors. Reception of DMT was coded in a binary format (1 – yes, 0 – no).

A stepwise multiple logistic regression analysis was performed. A logistic equation was used as a basis, which assumes that an adverse outcome (neurological disorders) is associated with factors according to the formula:

$$y=\exp(b_0+ b_{1-n}\times X_{1-n})/[1+\exp(b_0+ b_{1-n}\times X_{1-n})] \quad (1),$$

Where Y is the result of the probability of developing significant neurological manifestations (clinically significant disability) in patients with RRMS (EDSS≥3.5 points);

b_0 – coefficient indicating the value of the result in the case when the predictor is equal to 0;

b_{1-n} – regression coefficients showing how much the logarithm of the chance of developing significant neurological manifestations will change on average when the independent variable changes by one unit of its measurement;

x_{1-n} – predictor variables, indices of each patient for whom the prognosis is calculated.

Regardless of the values (x), the predicted value of the outcome (y) in this model will always range from 0 (absence of significant neurological manifestations) to 1 (development of significant neurological manifestations).

As a result of step-by-step inclusion of independent variables, it was possible to obtain parameters of the logistic regression equation for the onset of clinically significant neurological deficits (signs of disability) – from 3.5 points on the EDSS scale based on statistically significant predictors :

$$y=\exp(-171.27 + 626.56 \times x_1 + 4.58 \times x_2 -18.31 \times x_3)/$$
$$[1+ \exp(-171.27 + 626.56 \times x_1 + 4.58 \times x_2 -18.31 \times x_3)] \quad (2),$$

Where y is the result of the probability of developing significant neurological manifestations (clinically significant disability) in patients with RRMS (EDSS≥3.5 points);

x_1 – BCR index;

x_2 – number of BDI points;

x_3 – DMT reception: 1 – Yes/0 – No;

-171.27 – free term of the equation;

626.56 – regression coefficient β for the BCR index;

4.58 – regression coefficient β for the BDI index;

-18.31 – regression coefficient β for DMT reception.

According to the logistic regression analysis, the occurrence of a clinically significant neurological deficit, which is the clinical basis of disability (EDSS≥3.5 points), depends primarily on the degree of subcortical atrophy and the use of DMT.

According to multiple logistic regression analysis, statistically significant independent factors influencing the appearance of significant neurological manifestations, according to the adjusted, cleared from the influence of other factors, are: the degree of subcortical atrophy according to the BCR index (OR=26.2; 95 % CI 3.5–198.3), the level of depression according to BDI (OR=97.2; 95 % CI (3.4–2744.0), the use of DMT (OR=0.006; 95 % CI 0.001–0.045). An odds ratio of less than 1 indicates a protective effect of taking DMT.

OR shows that for each unit of increase in atrophy according to the BCR index, the chances of significant neurological manifestations (EDSS≥3.5 points) increase by 2.86 times (*p=0.049*); for each unit of growth of depression on the Beck scale – increase by 97.2 times (*p=0.007*), when taking DMT – decrease by 166.7 times (*p<0.001*).

The logistic regression equation (model) was evaluated using the Chi-square value (χ^2); percentage of concordant (concordant) – the share of observations correctly reclassified using the equation (the closer this indicator is to 100 %, the higher the quality of the model); Hosmer–Lemeshow test and ROC analysis.

The share of correct prediction of the patient's actual belonging to a particular group was 98.1 %. A high level of concordance indicates sufficient consistency between the real distribution of observations and the distribution based on logistic regression equation calculations.

The forecast equation constructed based on logistic regression (logistic model) was adequate according to the Chi-square indicator χ^2=114.3 ($p<0.001$), according to the Hosmer-Lemeshow test ($p=0.101$), as it showed a significant coincidence of real and calculated results.

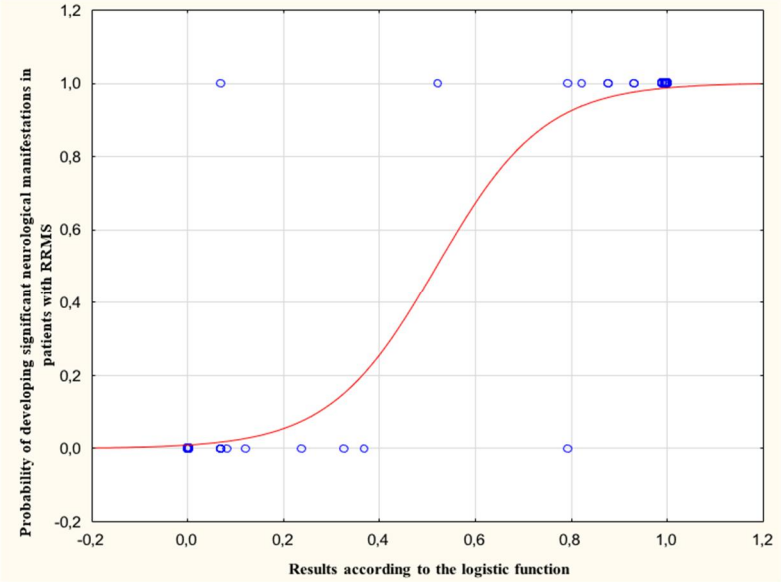

Fig. 1. The dependence of the probability of the development of significant neurological manifestations in patients with RRMS on the result calculated by the logistic equation

Based on the shape of the ROC curve and the area under it (AUC), the prognostic accuracy of the logistic regression equation was evaluated. It was determined that the prognostic model in the form of the logistic regression equation has excellent operational characteristics: the area under the ROC curve is 0.995 (95.0 % CI 0.956-1.000; $p< 0.001$ sensitivity 96.9 %, specificity 97.2 %.

Calculation according to the logistic equation and visualization of the theoretical values of the probability (P) of predicting significant neurological manifestations in patients with RRMS (Fig. 1) made it possible to propose a detailed prognosis scale.

A detailed scale for the prognosis of significant neurological manifestations in patients with RRMS (sign of disability: EDSS≥3.5 points) from the results obtained when calculating according to the logistic equation (2):

less than 0.2 – very low probability of developing significant neurological manifestations in patients with RRMS (P<5.4 %);

0.2–0.4 – low probability of developing significant neurological manifestations in patients with RRMS (5.4 %≤P<25.7 %);

0.4–0.53 – the moderate probability of developing significant neurological manifestations in patients with RRMS (25.7 %≤P<52.4 %);

0.53–0.65 – a high probability of developing significant neurological manifestations in patients with RRMS (52.4 %≤P<76.3 %);

0.65–0.78 – a very high probability of developing significant neurological manifestations in patients with RRMS (76.3 %≤P<91.4 %).

More than 0.78 – a very high probability of developing neurological disorders in patients with RRMS (P>91.4 %).

Therefore, according to the results of our study, it can be stated that the progression of neurological deficits and disability in patients with RRMS is influenced not only by the nature of the clinical course of the disease but also by neuropsychological changes and brain atrophy.

Thus, we found that psycho-emotional changes in patients with RRMS, namely increased anxiety and depression, can significantly affect the development of disability. It is advisable to assess the psycho-emotional state of patients when planning treatment, because correction of increased anxiety and reduction of depressive symptoms can potentially reduce disability and improve the quality of life of patients with RRMS.

Other researchers provide similar data. Thus, Masuccio F. et al., 2019, analyzing the development of depression in MS, conclude that the basis of depression in MS lies in neurobiological and structural-functional disorders of the brain, and, therefore, depression can be considered as a symptom of MS, which can affect on its course [4].

However, there is other data. So, Patten S. et al., 2017; Solaro C. Et al., 2018, prove that the neurological deficit in MS is the leading factor that leads to disturbances in the psycho-emotional state of patients [7, 9].

Calculation and evaluation of quantitative indicators of brain atrophy are often used to evaluate the effectiveness of DMT [2, 8]. Increased brain atrophy predicts increased neurological deficits and disability in patients with RRMS, which was demonstrated in our study.

Conclusions

1. The chances of developing significant neurological manifestations in patients with RRMS increase as the brain atrophy increases.

2. The index of subcortical atrophy has the best prognostic characteristics for predicting significant neurological deficit and progression of disability in patients with RRMS, among independent influencing factors.

3. Anxiety and depression negatively affect the course of RRMS and increase the chances of disability.

4. Taking DMT significantly reduces the chances of developing a significant neurological deficit in patients with RRMS.

Prospects for further research. It is promising to study the prognostic role of the total volume of demyelination foci and the index of general brain atrophy in predicting disability in MS patients.

References

1. Pinchuk VA, Delva M.Yu., Hryn KV. Prohnozuvannia perebihu rozsiyanoho sklerozu na pidstavi klinichnykh osoblyvostey debiutu u patsiyentiv Poltavskoyi oblasti. Ukrainskyi zhurnal medytsyny, biolohiyi ta sportu. 2023;8(1):146–150. doi: 10.26693/jmbs08.01.146 [in Ukrainian]

2. Cohan SL, Benedict RH, Cree BA, DeLuca J, Hua LH, Chun J. The two sides of Siponimod: Evidence for brain and immune mechanisms in multiple sclerosis. CNS Drugs. 2022;36(7):703–19. doi:10.1007/s40263-022-00927-z

3. Kern S, Geiger M, Paucke M, Kästner A, Akgün K, Ziemssen T. Clinical relevance of circadian melatonin release in relapsing-remitting multiple sclerosis. Journal of Molecular Medicine. 2019;97(11):1547–55. doi:10.1007/s00109-019- 01821-w

4. Masuccio FG, Gamberini G, Calabrese M, Solaro C. Imaging and depression in multiple sclerosis: A historical perspective. Neurological Sciences. 2021;42(3):835–45. doi:10.1007/s10072-020-04951-z

5. McGinley MP, Goldschmidt CH, Rae-Grant AD. Diagnosis and treatment of multiple sclerosis. JAMA. 2021;325(8):765. doi:10.1001/jama.2020.26858

6. Ohlmeier C, Gothe H, Haas J, Osowski U, Weinhold C, Blauwitz S, et al. Epidemiology, characteristics and treatment of patients with relapsing remitting multiple sclerosis and incidence of high disease activity: Real World evidence based on German claims data. PLOS ONE. 2020;15(5). doi: 10.1371/journal.pone.0231846

7. Patten SB, Marrie RA, Carta MG. Depression in multiple sclerosis. International Review of Psychiatry. 2017;29(5):463–72. doi:10.1080/09540261.2017.1322555

8. Rekik A, Aissi M, Rekik I, Mhiri M, Frih MA. Brain atrophy patterns in multiple sclerosis patients treated with natalizumab and its clinical correlates. Brain and Behavior. 2022;12(5). doi:10.1002/brb3.2573

9. Solaro C, Gamberini G, Masuccio FG. Depression in multiple sclerosis: Epidemiology, Aetiology, diagnosis and treatment. CNS Drugs. 2018;32(2):117– 33. doi:10.1007/s40263-018-0489-5

10. Sorensen PS, Sellebjerg F, Hartung H-P, Montalban X, Comi G, Tintoré M. The apparently milder course of multiple sclerosis: Changes in the diagnostic criteria, therapy and natural history. Brain. 2020;143(9):2637–52. doi:10.1093/brain/awaa145

11. Walton C, King R, Rechtman L, Kaye W, Leray E, Marrie RA, et al. Rising prevalence of multiple sclerosis worldwide: Insights from the atlas of MS, Third edition. Multiple Sclerosis Journal. 2020;26(14):1816–21. doi:10.1177/1352458520970841

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