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Predicting cognitive impairment and psycho-emotional disorders in Multiple Sclerosis patients according to MRI findings

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ABSTRACT

Objectives. The aim of our study was to assess the probability of cognitive impairment (CI) in general and in separate domains, depression, anxiety and sleep disorders onset depending on their association with MRI findings in patients with multiple sclerosis (MS).

Materials and methods. 137 patients with MS were enrolled into the study. All participants were divided into two groups: group A included study subjects with relapsing remitting multiple sclerosis (RRMS) and B consisted of patients with secondary progressive multiple sclerosis (SPMS).

Results. Participants with progressive forms of MS had a higher risk of CI development compare to the patients with RRMS (p=0,0361). Memory decline onset depended on the presence of the brain atrophy in combination with lesions of the parietal lobe (OR=2.74 (0.85-8.77), p <0.0001) in RRMS cases, furthermore, on presence of combined demyelination in temporal lobe with corpus callosum (OR=17.33 (2.92-103.02), p=0.0006) and parietal lobe separately (OR=7.5 (1.14-49.26), p=0.0239) in patients with SPMS.

Conclusions. CI and psycho-emotional disorders can be predicted by means of MRI findings and potentially prevented.

Keywords: multiple sclerosis, cognitive impairment, depression, MRI

INTRODUCTION

Multiple sclerosis (MS), a chronic inflammatory autoimmune neurodegenerative disease of the central nervous system (CNS), is a scourge of the modern society as it relatively rapidly results in a severe long-term disability of a vast number of working-age population (2.8 million people worldwide) due to the impact of the neurological and motor deficit along with cognitive impairment and psycho-emotional disorders on basic daily activities, not to mention the economic burden on the society [1,2,3]. Development of cognitive impairment and psycho-emotional disorders can be predicted already on the early stages of the disease by certain risk factors (age, type of MS course, education, cigarette smoking, marital status etc.) and by magnetic resonance imaging findings [4].

Presence of depressive disorder in patients with MS is associated with damage of the fronto-limbic connections: the bilateral anterior thalamic radiation, cingulum, superior longitudinal fasciculus and uncinate fasciculus [5]. Hence, depending on the localization of demyelination, cognitive impairment and psycho-emotional disorders in those patients can accompany motor and other neurological deficit, be present separately or in various combinations [6]. However, the relationships between cognitive impairment, depression, anxiety, sleep disorders and MR-findings, in MS patients demand further investigation.

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OBJECTIVE

The aim of our study was to assess the probability of cognitive impairment (CI) in general and in separate domains, depression, anxiety and sleep disorders onset depending on their association with MRI findings in patients with MS.

MATERIALS AND METHODS

The given study enrolled one hundred and thirty-seven patients diagnosed with MS (102 females and 35 males) aged from 22 to 60 years (mean age: 42.6±9.4). According to the MS type, all the patients were divided into two groups: group A – study subjects with relapsing remitting multiple sclerosis (RRMS) (n=106; 81 females and 25 males aged from 22 to 67 years; mean age: 41.8±10.7) and B – patients with secondary progressive multiple sclerosis (SPMS) (n=31; 21 females and 10 males aged from 28 to 69 years, mean age: 47.2±13.6). Mean disease duration in group A was 10.3±8.5 years and in group B – 13.5±9.2.

The survey subjects were diagnosed RRMS according to McDonald's Criteria 2017 [7]. A medical history was obtained from each study participant. The examination included a standard clinical evaluation, neurological examination, the application of neuropsychological questionnaires, neurovisualization study (MRI scan of brain) and laboratory tests (complete blood count, biochemical parameters, TSH). The disability level in MS patients was evaluated by means of Kurtzke's Expanded Disability Status Scale (EDSS), where mild disability equals 1-3.5 points, moderate – 4-6 points and 6.5-8 stand for severe disability [8]. The Montreal Cognitive Assessment (MoCA) was applied to evaluate presence and severity of CI. The MoCA includes six subcategories according to the domains: memory (M), language (L), attention (A), abstract thinking (AT), visual-spatial and executive functions (VS/EF). The scale score was interpreted as: 30-26 points – no CI; 25-18 points – mild CI; <18 points – severe CI [9]. Beck Depression Inventory (BDI) was applied to find the presence and asses the severity of depression. The scale consists of 21 items that tap major depression symptoms in accordance to diagnostic criteria listed in the Diagnostic and Statistical Manual for Mental Disorders. Each answer is scored from 0 to 3 points. Mean score 0-9 indicates absence of depression, 10-18 – mild depression, 19-29 – moderate depression and 30-63 – severe depression [10]. To assess the anxiety level Hamilton Anxiety Rating Scale (HAM-A) was used. This scale includes 14 items depicting psychological and physical signs of anxiety. Every answer is evaluated from 0 to 4 points. Mean score 0-13 indicates of absence of anxiety, 14-17 – presence of mild anxiety, 18-24 – presence of moderate anxiety, 25-30 stands for presence of severe anxiety [11]. Sleep quality was evaluated by means of The Pittsburgh Sleep Quality Index (PSQI). The questionnaire consists of 24 items, answers to which can be assessed from 1 to 4. Mean score can be interpreted as: 0-15 points stands for lack of sleep disorders, 16-25 – presence of mild sleep disorders, 26-35 – moderate and 36-45 – severe sleep disorders [12]. All participants were screened for the level of education.

The participants were excluded from the study if they were younger than 18, had progressive forms of MS, stage of exacerbation of RRMS or severe disability (EDSS score: 6.5 – 8 points), severe depression, pelvic disorders, pregnancy, cerebrovascular pathology, as well as patients treated with corticosteroids and INF-β, which could alter the study's parameters.

All the study subjects provided written informed consent and the study was approved by the Institutional Ethics Committee.

All statistical data was processed by means of Graph Pad Prism version 9 software. Student's t-test (t) was applied for evaluating credibility between mean quantitative positions of two samples. Proportions were compared using $\chi 2$. Relationships between different indicators were assessed using the Pearson's correlation coefficient (r) according to statistical distribution. A $p<0.05$ value was considered statistically significant.

RESULTS

We evaluated the data on the lesions' location in both study groups in order to define the clinical-neurovisualization interrelation in MS patients with cognitive disorders, depression, anxiety and sleep disorders. 62% (n=66) of patients of the group A had cognitive impairment, 51% (n=54) – depression, 69% (n=73) – anxiety and 38% (n=41) – sleep disorders. As for the group B, 68% (n=21) study subjects suffered from cognitive impairment, 45% (n=14) – from depression, 77% (n=24) – from anxiety and 55% (n=17) experienced sleep disorders.

The participants' MRI results demonstrated a variety of demyelination lesions locations. Among patients of the group B in comparison to the group A brain atrophy (p=0,0008), lesions of parietal (p=0,0109), occipital (p=0,0055) lobes and periventricular zone (p=0,0001), simultaneous presence of brain atrophy and frontal lobe lesions (p=0,0021), combined lesions of corpus callosum and frontal lobe (p=0,0327), combined lesions of parietal lobe and corpus callosum (p=0,0279) and brain atrophy in combination with lesions of temporal lobe (p=0,0066) were found considerably more frequently (Table 1).

TABLE 1. Distribution of demyelination in the different brain areas among the patients of both clinical groups (n, %)

Affected part of the brain	Group A (n=106)	Group B (n=31)	P
Frontal lobe	73 (69)	24 (77)	0.3570
Temporal lobe	54 (51)	18 (58)	0.4849
Parietal lobe	41 (38)	20 (64)	0.0109 *
Occipital lobe	3 (2)	5 (16)	0.0055*
Corpus callosum	73 (69)	24 (77)	0.3570
Brain atrophy	36 (34)	21 (68)	0.0008 *
Periventricular zone	99 (93)	28 (90)	0.0001*
Cerebellum	58 (55)	18 (58)	0.7415
Brainstem	44 (41)	16 (51)	0.3186
Frontal lobe + Brain atrophy	27 (25)	17 (55)	0.0021*
Frontal lobe + Corpus callosum	42 (39)	19 (61)	0.0327*
Temporal lobe + Corpus callosum	44 (41)	16 (51)	0.3186
Parietal lobe + Corpus callosum	32 (30)	16 (51)	0.0279 *
Temporal lobe + Parietal lobe	26 (24)	8 (26)	0.8848
Frontal lobe + Temporal lobe + Parietal lobe	18 (17)	8 (26)	0.2704
Temporal lobe + Brain atrophy	17 (16)	12 (39)	0.0066*
Parietal lobe + Brain atrophy	34 (32)	14 (45)	0.1205

*P <0,05

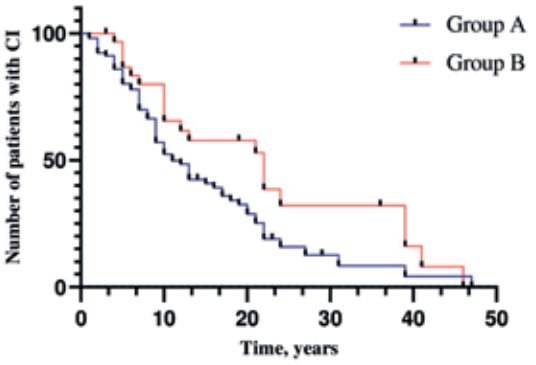

FIGURE 1. Probability of the cognitive impairment development among participants of both clinical groups.

FL – frontal lobe, TL – temporal lobe, PL – parietal lobe, CC – corpus callosum, BA – brain atrophy

Odds ratio (OR) with 95% confidence interval risk assessment and Kaplan–Meier methods were applied for a prognostic evaluation of cognitive impairment, depression, anxiety and sleep disorders development depending on location of demyelination lesions in the brain.

We established that patients with SPMS had a substantially higher probability of cognitive impairment development comparing to the patients with RRMS (p=0,0361) (Figure 1).

In the group A tendency towards CI development was considerably higher in case of affected corpus callosum (OR=2.08 (0.89-4.86), p=0.0867), in presence of lesions in frontal lobe and corpus callosum simultaneously (OR=2.04 (0.92-4.53), p=0.0793), in case of brain atrophy in combination with plaques in the frontal lobe (OR=1.73 (0.68-3.35), p=0.2435) and on the background of combined lesions of frontal and temporal lobes (OR=1.61 (0.68-3.78), p=0.2741)).

Concerning the group B, a potential risk of CI onset was significantly higher in case of combined lesions of temporal and occipital lobes (OR=4.5 (0.47-42.97), p=0.1652), in presence of demyelination in parietal lobe (OR=2.5 (0.53-11.89), p=0.2438), on the background of simultaneously affected frontal and temporal lobes (OR=2.0 (0.43-9.26), p=0.3719), in case of combined lesions of frontal and parietal lobes (OR=2.0 (0.43-9.26), p=0.3719), and in case of demyelination in frontal lobe separately OR=1.82 (0.32-10.34), p=0.4954). Hence, significant impact demyelination localization on the risk of CI development was not observed in both groups of patients.

Risk of separate cognitive domains impairment in clinical groups was also carefully estimated. In the group A probable onset of memory decline was significantly associated with the combination of brain atrophy and parietal lobe lesions (OR=2.74 (0.85-8.77), p <0.0001). Brain atrophy in combination with frontal lobe plaques (OR=1.94 (0.7-5.36), p=0.1961), affected temporal lobe combined with brain atrophy (OR=1.34 (0.4-4.5), p=0.6336), presence of brain atrophy alone (OR=1.94 (0.77-4.91), p=0.1554) and damage of corpus callosum separately (OR=1.85 (0.77-4.42), p=0.1651) formed a tendency of memory decline among the study participants (Figure 2). Probability of memory disorders was noticeably increased in case of brain atrophy combined with parietal lobe demyelination (p= 0.0029) (Figure 3).

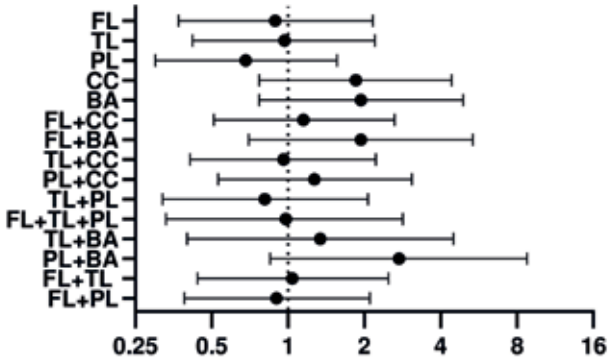

FIGURE 2. Probability of memory decline development in the patients with RRMS (risk assessment with 95% – OR (95%CI)).

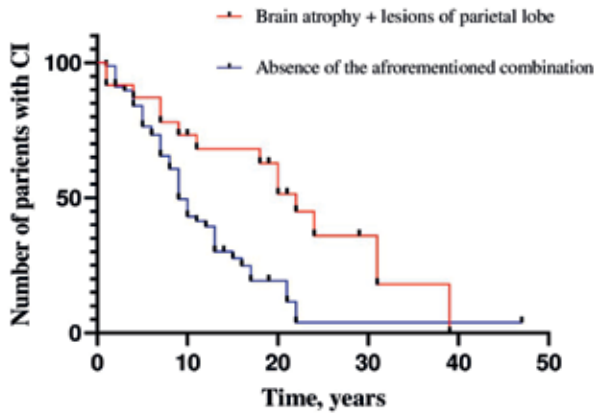

FIGURE 3. Probability of memory decline development in the patients with RRMS.

FL – frontal lobe, TL – temporal lobe, PL – parietal lobe, CC – corpus callosum, BA – brain atrophy

A tendency towards attention impairment was detected on the background of parietal lobe lesions (OR=2.23 (0.97-5.09), p=0.0559), simultaneously affected temporal and parietal lobes (OR=2.18 (0.87-5.45), p=0.1308), combined demyelination of frontal, temporal and parietal lobes (OR=2.0 (0.73-5.48), p=0.1732) and brain atrophy in combination with affected parietal lobe (OR=1.93 (0.76-4.86), p=0.1627) among the study subjects of the group A.

In the group A significantly high risk of executive functions/visual-spatial orientation development was observed in case of simultaneously affected frontal and parietal lobes (OR=3.68 (1.36-10.0), p=0.0080). Higher probability of the onset of the executive functions disorders was associated with combined lesions in the frontal, temporal and parietal lobes (OR=2.67 (0.72-9.9), p=0.1313), simultaneously affected frontal and temporal lobes (OR=2.3 (0.88-6.01), p=0.0840), combination of parietal lobe and corpus callosum plaques (OR=2.3 (0.88-6.01), p=0.0840) and corpus callosum demyelination separately (OR=1.98 (0.82-4.76), p=0.1238) (Figure 4).

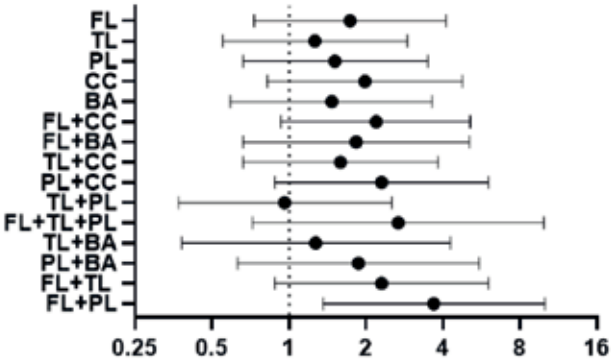

FIGURE 4. Probability of executive functions disorders development in the patients with RRMS (risk assessment with 95% – OR (95%CI)).

FL – frontal lobe, TL – temporal lobe, PL – parietal lobe, CC – corpus callosum, BA – brain atrophy

Chances of the verbal disorders occurrence among participants of the group A increased in case of the combined lesions of frontal and parietal lobes (OR=1.92 (0.6-4.45), p=0.1248), demyelination of parietal lobe and corpus callosum (OR=1.71 (0.73-4.01), p=0.2161), corpus callosum (OR=1.53 (0.6-3.89), p=0.3699) and frontal lobe separately (OR=1.38 (0.56-3.44), p=0.5346).

In the group A tendency of the abstract thinking disorders was connected with the presence of demyelination in corpus callosum (OR=1.86 (0.79-4.34), p=0.1504), combined lesions parietal lobe and corpus callosum (OR=1.87 (0.83-4.21), p=0.1310), simultaneously affected frontal lobe and corpus callosum (OR=1.85 (0.85-3.99), p=0.1181) and parietal lobe plaques separately (OR=1.58 (0.73-3.41), p=0.2404).

As for the group B, development of memory decline was more significantly probable in case of combined lesion of corpus callosum and temporal lobe (OR=17.33 (2.92-103.02), p=0.0006) and demyelination lesions in the parietal lobe alone (OR=7.5 (1.14-49.26), p=0.0239). A tendency towards memory impairment was observed on the background of lesions in the temporal and parietal lobes (OR=2.47 (0.25-24.46), p=0.4285), simultaneously affected frontal, temporal and parietal lobes (OR=2.47 (0.25-24.46), p=0.4285), combination of frontal and parietal lobe lesions (OR=3.5 (0.56-21.81), p=0.1656) and in case of parietal lobe and corpus callosum demyelination (OR=3.5 (0.56-21.81), p=0.1656) (Figure 5).

Among the patients of the group B, risk of attention decline was associated with presence of demyelination lesions in parietal lobe (OR=3.33 (0.34-32.96), p=0.2834), in temporal and parietal lobes simultaneously (OR=4.0 (0.61-24.46), p=0.1315), in frontal, temporal and parietal lobes (OR=4.0 (0.61-24.46), p=0.1315), in frontal and parietal lobes concurrently (OR=2.17 (0.33-14.06), p=0.4113) and in case of combined lesions of parietal lobe and corpus callosum (OR=2.17 (0.33-14.06), p=0.4113).

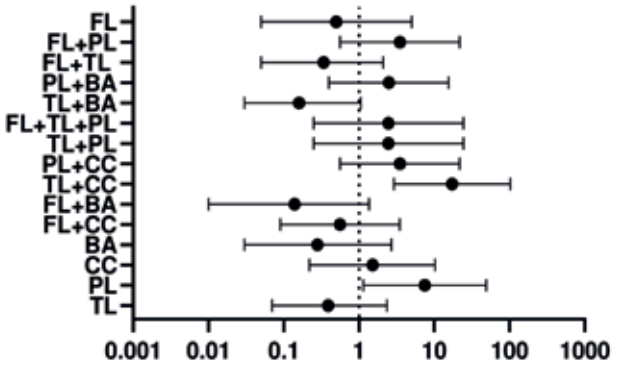

FIGURE 5. Probability of memory decline development in the patients with SPMS (risk assessment with 95% – OR (95%CI)).

FL – frontal lobe, TL – temporal lobe, PL – parietal lobe, CC – corpus callosum, BA – brain atrophy

Probability of executive functions/visual-spatial orientation impairment onset was higher in case of demyelination in frontal and temporal lobes (OR=4.95 (0.99-24.87), p=0.0443) in group B. A greater risk of executive functions/visual-spatial orientation disorders was associated with demyelination lesions in temporal and parietal lobes (OR=4.5 (0.47-42.97), p=0.1656), simultaneously affected frontal, temporal and parietal lobes (OR=4.5 (0.47-42.97), p=0.1656), in case of lesions in parietal lobe and corpus callosum (OR=5.0 (0.74-33.78), p=0.7393) and separately affected frontal lobe (OR=4.0 (0.69-23.23), p=0.1094).

An increased risk of verbal disturbances onset was associated with presence of lesions in frontal lobe and corpus callosum simultaneously (OR=6.0 (0.62-57.68), p=0.0920), frontal lobe (OR=2.47 (0.25-24.46), p=0.4285) and corpus callosum affected separately (OR=2.47 (0.25-24.46), p=0.4285) and in case of combined lesions of frontal and temporal lobes (OR=2.95 (0.48-18.34), p=0.2331) in the patients of the group B.

In the group B probability of abstract thinking disorders development was connected with the simultaneous presence of lesions in temporal and parietal lobes (OR=4.5 (0.47-42.97), p=0.1652), concurrently affected frontal, temporal and parietal lobes (OR=4.5 (0.47-42.97), p=0.1652) and in case of demyelination of frontal and temporal lobes (OR=3.79 (0.75-19.04), p=0.0966).

Furthermore, we have assessed the probability of pshycho-emotional disorders occurrence depending on the location of demyelination lesions in both clinical groups. In the group A risk of depression onset was greater in case of presence of brain atrophy and lesions of parietal lobe (OR=1.84 (0.72-4.45), p=0.1979), combination of brain atrophy and lesions of frontal lobe OR=1.71 (0.71-4.12), p=0.2279) and separately affected corpus callosum (OR=1.51 (0.66-3.49), p=0.3300). As for the group B, probability of depression development was associated with lesions of corpus callosum (OR=3.24 (0.57-18.38), p=0.1735), combination of demyelination in temporal lobe and corpus callosum (OR=2.63 (0.57-12.0), p=0.2077), separately affected temporal lobe (OR=2.23 (0.5-10.0), p=0.2913), combined lesions of frontal lobe and corpus callosum (OR=1.55 (0.34-6.94), p=0.5675) and in case of simultaneously damaged frontal and temporal lobes (OR=1.47 (0.33-6.43), p=0.6109).

Significantly higher chances of anxiety onset depended on the presence of lesions in frontal and temporal lobes (OR=2.67 (1.15-6.17), p=0.0202) in the group A. A tendency towards anxiety development was observed in case of demyelination in temporal lobe (OR=1.65 (0.72-3.77), p=0.2381) and simultaneously affected parietal lobe and corpus callosum (OR=1.57 (0.64-3.86), p=0.3282) (Figure 6). In the group B greater risk of anxiety onset was associated with lesions in the corpus callosum (OR=1.52 (0.22-10.3), p=0.6666), parietal lobe (OR=1.05 (0.19-5.76), p=0.9552), and combination of temporal lobe lesions and brain atrophy (OR=0.8 (0.14-4.42), p=0.7979).

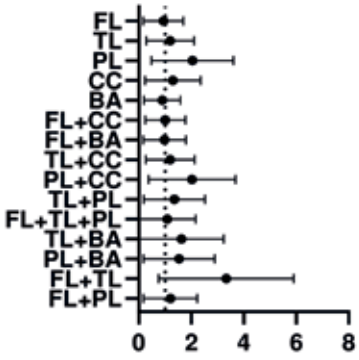

FIGURE 6. Probability of anxiety development in the patients with RRMS (risk assessment with 95% – OR (95%CI)).

In the group A sleep disorders were more likely to develop on the background of localization of demyelination in corpus callosum B (OR=1.3 (0.55-3.09), p=0.5496), brain atrophy combined with demyelination lesions in the temporal lobe (OR=0.84 (0.29-2.48), p=0.7545) and combined lesions in parietal lobe and corpus callosum (OR=1.01 (0.44-2.31), p=0.9746). Concerning the group B, a tendency towards sleep disorders onset was detected in case of brain atrophy presence (OR=4.67 (0.92-23.79), p=0.0552), brain atrophy in combination with frontal lobe lesions (OR=4.32 (0.95-19.58), p=0.0522), brain atrophy in combination with temporal lobe lesions (OR=2.22 (0.5-9.96), p=0.2930) and corpus callosum affected separately (OR=1.87 (0.34-10.25), p=0.4691).

DISCUSSION

Numerous prior studies focused on possibilities to predict the onset of hidden MS symptoms based on clinical picture and various risk factors, though far less draw attention to MRI findings as predictors of those.

Our study revealed that people with SPMS were more prone to develop cognitive impairment comparing to the ones with RRMS, which is consistent with the results of Eijlers A.J.C. et al., who confirmed such a prognosis [13]. Ziccardi S. et al. stated that brain atrophy was a valid predictor of cognitive decline in the future [14], which coincided with our findings. Several studies stated that probability of memory impairment was associated with presence of demyelination in hippocampus, anterior cingulate cortex (as part of fronto-parietal network), thalamus and dorsolateral prefrontal area [15,16]. Therefore, the current research revealed that memory impairment onset considerably depended on the presence of the brain atrophy in combination with lesions of the parietal lobe in RRMS cases, furthermore, on presence of combined demyelination in temporal lobe with corpus callosum and parietal lobe separately in patients with SPMS. According to Du X.F. et al., lesions of frontal lobe played a key role in the development of executive functions disorders in patients with RRMS [16]. Similarly, our study uncovered the connection between onset of executive functions impairment and lesions of frontal and parietal lobes. The survey of Blecher T. et al. determined the relation between the lesions of the left fronto-temporal arcuate fasciculus, bilateral inferior fronto-occipital fasciculus and bilateral frontal aslant tract with verbal fluency issues in patients on the early stages of MS [17]. Whereas, this study established a link between a higher risk of verbal fluency disorders development and demyelination of frontal lobe and corpus callosum simultaneously SPMS patients.

Alerting function reportedly was associated with demyelination in the frontal, parietal and visual cortices [18], meanwhile, we did not detect a connection between location of plaques with probable attention decline in both clinical groups.

According to previous data, signs of depression had connections with demyelination of temporal lobe, middle cingulate and middle frontal gyri [19], nevertheless, the current survey did not detect any interrelations between localization of lesions and probable depression onset in both clinical groups. Ellwardt E. uncovered that presence of anxiety was connected with localization of lesions or atrophy in the prefrontal cortex, amygdala and hippocampus [20], whereas, we found a connection between anxiety onset and demyelination in the frontal and temporal lobes only in the RRMS participants. In current research we established that a risk of sleep disorders development was connected with the presence of brain atrophy alone and in combination with lesions in frontal lobe in SPMS patients.

Limitations

There are a few limitations of this study. Firstly, the survey tools used were of the self-report type, so there is always a risk of self-report bias. Secondly, this study did not include a control group.

CONCLUSIONS

Mild and hidden symptoms are common for patients with multiple sclerosis and contribute into the overall health burden. The results of this study indicate that it is possible for a clinician to predict onset of certain mental issues, which can give a head start to prevent their development and therefore improve patients' quality of life. Based on these findings, further research should address some of the methodological limitations of past studies. Objective measurement of cognitive and psycho-emotional disorders, although time consuming and costly, are likely to achieve more substantial results.

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