TEACHING SCIENTIFIC COUNCIL OF THE FACULTY OF MEDICINE

UNIVERSITY OF BELGRADE

At the meeting of the **Teaching Scientific Council** of the Faculty of Medicine in Belgrade, held on June 5, 2024, No 19/XXVI-1/3-AJ, the Evaluation Committee was appointed for the assessment of the completed PhD thesis entitled:

„ **Investigation of the prevalence, epidemiological and clinical characteristics of familial occurrence of multiple sclerosis in the population of Belgrade**“

written by the candidate Aleksa Jovanović, MD. The mentor of the thesis is Professor Tatjana Pekmezović, MD, PhD, and co-mentors are Professor Ivana Novaković, MD, PhD, and Professor Šarlota Mesaroš, MD, PhD.

The members of the appointed Evaluation Committee are:

1. Prof. dr Jelena Drulović, Faculty of Medicine, University of Belgrade
2. Ass. Prof. dr Gorica Marić, Faculty of Medicine, University of Belgrade
3. Prof. dr Borut Peterlin, Medical Faculty, University of Ljubljana, Ljubljana, Slovenia

Based on the analysis of the submitted PhD thesis, the Evaluation Committee submits to the Scientific Council of the Faculty of Medicine the following

REPORT

A) The contents of the thesis

The PhD thesis of Aleksa Jovanović, MD is written on 74 pages and is divided into the following sections: Introduction, Objectives, Material and Method, Results, Discussion, Conclusions and References. The thesis contains a total of 51 tables and two figures. The doctoral dissertation contains a Summary, both in English and in Serbian, as well as the Candidate's biography, information about the Assessment Committee, and a list of abbreviations used in the text.

In the **Introduction** section, multiple sclerosis (MS) was first defined, its significance as the leading non-traumatic cause of disability in young adults was described, and the prevalence of MS in the world and Europe was briefly outlined along with the defined phenotypes of MS. Then, the role of genetic factors in the etiology of MS was briefly described, and the definitions of familial multiple sclerosis (fMS) were provided.

Next, the most important features of MS pathophysiology were discussed, the clinical presentation of MS, including symptoms and signs, was described, and the phenotypes of MS were detailed. Key diagnostic techniques for MS and diagnostic criteria for MS were described. Following this, the basic principles of therapy for MS patients and the prognosis for MS patients were outlined, including brief descriptions of the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Severity Score (MSSS).

Furthermore, the epidemiology of MS was described in more detail, including its distribution, demographic characteristics of individuals with MS, and etiology, which covered environmental and genetic risk factors for the onset of MS. At the end of the introduction, the features of fMS were described in more detail, such as its prevalence, distribution among family members, differences in clinical presentation and prognosis between fMS and sporadic MS (sMS), and a brief description of the anticipation phenomenon was provided.

The **Objectives** of the study were clearly defined. They include the assessement of the prevalence of fMS in the population of Belgrade, determining risk factors for the onset of fMS compared to sMS and controls, identifying predictive factors associated with disease outcomes in individuals with fMS and sMS, and characterizing rare gene variants in patients with fMS using whole-exome sequencing.

In the **Materials and Methods** section, it was stated that the research included the design of four observational studies: a cross-sectional study, two case-control studies, and a retrospective cohort study, conducted from 2021 to 2023 at the Neurology Clinic of the University Clinical Center of Serbia (UCCS) and at the Clinical Institute for Medical Genetics, University Medical Center Ljubljana, Ljubljana, Slovenia.

The cross-sectional study aimed to assess the prevalence of fMS in Belgrade, based on the Belgrade population MS registry, which has existed since 1996 at the Neurology Clinic of UCCS. It is mentioned that the registry contains information on all patients diagnosed with MS in Belgrade, including demographic and clinical characteristics. The definition used for

fMS was an MS case with a first, second, or third-degree relative with MS. Patients with registered family members with MS were interviewed to create a pedigree for each proband from fMS families. The prevalence of fMS was calculated as the proportion of fMS cases among all MS cases in the registry. Comparisons of demographic and clinical characteristics between patients with fMS and sMS in the registry were performed using the chi-square test, t-test, and Mann-Whitney U test.

The case-control study aimed to investigate risk factors for the development of fMS and was conducted at the Neurology Clinic of UCCS from March 2021 to January 2023. Three groups were formed for analysis: the fMS group, the sMS control group, with subjects individually matched to the fMS group by gender, age (±2 years), and disease form, and a healthy control (HC) group of healthy spouses. Inclusion criteria for the fMS group were the presence of a first-, second-, or third-degree relative with MS and age ≥18 years. A specific questionnaire, previously translated, validated, and culturally adapted for use in the Serbian population, was used for data collection. The first part of the questionnaire contained questions about participants' demographic data, the second part about sun exposure, the third part about diet, the fourth part about personal and family medical history, the fifth part about lifestyle-related risk factors, and the last part about hormonal factors, completed only by women. Logistic regression was used for data analysis, and odds ratios (OR) with corresponding 95% confidence intervals (95% CI) were calculated.

The retrospective cohort study aimed to assess predictive factors associated with disease outcomes in fMS and sMS, using patient medical histories from the Neurology Clinic of UCCS. All participants were evaluated for MS progression and levels of physical disability (EDSS and MSSS) from the onset of MS symptoms to the end of follow-up. MSSS was calculated based on the last EDSS score and disease duration. Diagnostic delay was calculated as the difference between the age at diagnosis and the age at the onset of symptoms.

The case-control study aimed at characterizing rare and unusual gene variants in fMS patients investigated rare gene variants in individuals with fMS in the Serbian population. The case group included patients with fMS having a first-degree relative with MS, while the control group included patients with other neurological diseases excluding MS. Both groups were recruited at the Neurology Clinic, UCCS, and exclusively included individuals of Serbian ethnicity. Whole-exome sequencing (WES) was used, and the burden of rare variants was analyzed using a generalized linear model (GLM) in the R statistical environment, with

correction for the false discovery rate (FDR).

In the **Results** section, all obtained results are described in detail and clearly presented with both tabular and graphical displays.

The **Discussion** is written systematically, clearly, and comprehensively, presenting data from other studies with a comparative review of the doctoral dissertation's obtained results for each finding.

The **Conclusions** succinctly present the most important findings derived from the results of the study.

The **Bibliography** contains a list of 263 references.

B) Verification of Originality of the Doctoral Dissertation

Based on the Regulation on the Procedure for Checking the Originality of Doctoral Dissertations Defended at the University of Belgrade (Serbian – *Pravilnik o postupku provere originalnosti doktorskih disertacija koje se brane na Univerzitetu u Beogradu*) and the findings in the report from the iThenticate program, which was used to check the originality of the doctoral dissertation "**Investigation of the prevalence, epidemiological and clinical characteristics of familial occurrence of multiple sclerosis in the population of Belgrade**" by Dr. Aleksa Jovanović, the total text similarity amounts to 22% (Similarity index). This level of similarity is entirely expected because Dr. Aleksa Jovanović's dissertation is written in English, in a monographic format. The content of the papers resulting from the doctoral dissertation, which were previously published, is included in the dissertation text, with tables and graphs presented in the identical form as in the published papers, with minimal changes for consistent formatting and style of the dissertation, and with clear citation of sources, in accordance with the Regulation on Doctoral Academic Studies at the University of Belgrade – Faculty of Medicine.

The percentage of text overlap between the dissertation and the first and second paper is 3% and 2%, respectively.

The remaining overlap (17%) is predominantly due to the names of citations, personal names, the use of statistical techniques, generally accepted phrases, incidental overlaps of individual words or numbers, and citations, so-called commonplaces and data, which is in accordance

with Article 9 of the Regulation on the Procedure for Checking the Originality of Doctoral Dissertations Defended at the University of Belgrade ("Gazette of the University of Belgrade", No. 204/18).

C) A brief description of the obtained results

On the prevalence day, June 30, 2022, there were 2765 persons with MS (PwMS) registered in the Belgrade population MS registry, including 1927 women (69.7%) and 838 men (30.3%). The average age of PwMS in the registry was 56.3±14.4 years. The distribution of PwMS by MS phenotype shows that 1689 (63.2%) patients have relapsing-remitting MS (RRMS), 638 (23.8%) have secondary progressive MS (SPMS), and 347 (13.0%) have primary progressive MS (PPMS).

Among all patients in the registry, there were 178 cases of fMS (prevalence of 6.4%). The prevalence of fMS was similar between genders: 6.5% in women and 6.2% in men. Compared to sMS cases, fMS cases were younger (48.4±13.9 vs. 56.9±14.2 years), had an earlier disease onset (30.4±9.5 vs. 32.3±10.1 years), and shorter disease duration (18.3±11.9 vs. 24.6±12.3 years). Additionally, the median EDSS score was lower in fMS cases (2.5, range 1.0-6.0) compared to sMS cases (4.0, range 2.0-6.5). Interviews were conducted with 96 fMS probands to obtain their full pedigrees. The highest prevalence of MS among relatives of fMS probands was observed in sisters (27.1%), mothers (22.9%), and daughters (21.7%) of fMS probands, while the lowest prevalence was found in grandfathers (1.0%). The prevalence of fMS was higher among female relatives in all categories compared to male relatives. Comparative analysis of fMS cases between generations did not show statistically significant differences in gender distribution, progression index, or MS phenotype between the older and younger generations. However, the younger generation had an earlier onset of symptoms, with an average age of 25.8±7.2 years, compared to 35.7±11.6 years in the older generation ($p<0.001$). After adjusting for different lengths of follow-up, the difference in the age of symptom onset remained statistically significant, but with a smaller difference (symptom onset at 30.0±7.9 years for the younger generation compared to 36.4±11.9 years for the older generation, $p=0.04$).

It is stated that in the case-control study aiming to investigate risk factors for the development of fMS, 393 respondents completed the questionnaire (131 fMS, 131 sMS, and 131 HC). None of the factors related to skin phototype stood out as a risk factor for fMS or sMS, nor did summer sun exposure, while winter sun exposure at ages 16-25 emerged as a protective factor

for fMS compared to HC, but this association disappeared after controlling for potential confounders. Additionally, performing professional activities outdoors or equally indoors and outdoors was shown to be a protective factor for both fMS and sMS compared to HC, with these results remaining statistically significant for ages 21-25 and 26-30 even after controlling for potential confounders (fMS vs. HC – adjusted OR 0.38, 95% CI 0.18-0.78 for age 21-25, adjusted OR 0.33, 95% CI 0.15-0.69 for age 26-30; sMS vs. HC – adjusted OR 0.47, 95% CI 0.24-0.92 for age 21-25, adjusted OR 0.51, 95% CI 0.26-0.99 for age 26-30). Weekend sun exposure, UV lamp use, and the use of protective creams were not associated with the risk of fMS or sMS.

Regarding food consumption factors at ages 13-19, seafood consumption was shown to be a protective factor for fMS compared to sMS (adjusted OR 0.50, 95% CI 0.26-0.95), while fresh fish (adjusted OR 0.52, 95% CI 0.30-0.90) and trout (adjusted OR 0.57, 95% CI 0.33-0.95) consumption were protective factors for fMS compared to HC. Trout consumption was also shown to be a protective factor for sMS compared to HC (adjusted OR 0.56, 95% CI 0.32-0.99).

Frequent bottled water consumption at ages 13-19 was shown to be a risk factor for fMS (adjusted OR 4.95, 95% CI 1.77-13.88) and sMS (adjusted OR 3.40, 95% CI 1.12-10.31) compared to HC.

Regarding breastfeeding practices, exclusive breastfeeding for 7-9 months (adjusted OR 0.47, 95% CI 0.28-0.80) and over 10 months (adjusted OR 0.48, 95% CI 0.29-0.81) were protective factors for fMS compared to sMS. On the other hand, the use of cow's milk (adjusted OR 1.97, 95% CI 1.13-3.44) and powdered milk (adjusted OR 2.07, 95% CI 1.07-4.02) in early childhood increased the risk of fMS compared to sMS.

When compared to HC, it was shown that a positive personal history of infectious mononucleosis increased the risk for fMS (OR 2.69, 95% CI 1.01-7.18) and sMS (OR 3.11, 95% CI 1.18-8.15). No other anamnesis data showed an association with the risk of fMS or sMS. A family history of psoriasis was associated with an increased risk of fMS compared to HC, but this association disappeared after adjusting for potential confounders.

A higher self-reported body figure at age 30 and having ≥2 pregnancies were shown to be risk factors for fMS and sMS compared to HC, but these associations disappeared after adjusting

for potential confounders.

In the matched retrospective cohort study involving 262 patients (131 fMS and 131 sMS), no statistically significant differences were found in any clinical variables between the fMS and sMS cohorts. Although the average age at symptom onset was lower in the fMS cohort compared to the sMS cohort, this difference did not reach statistical significance (29.9 ± 9.3 vs. 31.3 ± 11.0 years, $p = 0.548$).

In the case-control study investigating rare gene variants in fMS, nine rare variants predicted pathogenic were identified in the fMS group. Among them, seven variants were missense mutations with a moderate predicted impact on gene function, and two were stop-gain mutations, estimated to have a high impact on gene function. After FDR correction, no statistically significant enrichment of these variants was found in the fMS group. However, five rare variants: CLEC16A chr16:11126134_G/A, ALPK2 chr18:58523972_G/T, TYK2 chr19:10378250_C/T, SLC9B1 chr4:102932166_T/C, and WWOX chr16:78115103_C/T were found exclusively in fMS patients.

D) Comparative analysis of the doctoral thesis with the results from the literature

So far, no studies have been conducted in the Republic of Serbia aimed at examining the differences in risk factor profiles between fMS and sMS, nor have there been any studies investigating the burden of rare gene variants in individuals with fMS in our population. Additionally, in foreign literature, the approach of separating risk factors for the onset of MS between familial and sporadic forms of the disease has not been described thus far.

The prevalence of fMS of 6.4% found in this study is consistent with literature data, where a wide range of fMS prevalence has been reported, from 2.2% in Hungary to nearly 33% in Saskatchewan, Canada (Fricska-Nagy et al., 2007; Hader and Yee, 2014). Results of a meta-analysis published in 2021 estimated the global prevalence of fMS at 11.8% (95% CI: 10.7-13.0%) (Ehtesham, Rafie, and Mosallaei, 2021). This systematic review found similar prevalence among genders (15.4% in women and 13.7% in men), which aligns with the findings of this study (6.5% in women and 6.2% in men) (Ehtesham, Rafie, and Mosallaei, 2021).

The prevalence of MS among proband relatives was used to approximate the risk for the onset of MS among relatives. The highest prevalence of MS was observed in sisters of fMS

probands (27.1%), followed by mothers (22.9%) and daughters (21.7%). Similar findings were obtained in an Australian study (O'Gorman et al., 2011), where the highest crude risk for MS was observed in sisters of probands (2.88%), followed by mothers (1.09%), daughters (0.94%), and brothers (0.94%) (O'Gorman et al., 2011). Another study conducted in the UK also found that sisters were the family members of probands with the highest crude risk for MS (3.74%), followed by brothers (2.65%), mothers (2.08%), fathers (1.96%), and daughters (1.01%) (Robertson et al., 1996).

In the case-control study involving 131 fMS cases, 131 sMS cases, and 131 HC, factors related to skin phototype and sun exposure until the age of 30, which could influence vitamin D synthesis in the skin due to its impact on the risk of developing MS, were investigated. These factors included skin, eye, and hair color, tanning response, amount of outdoor activity during winter, summer, and weekends, place of professional activity (indoors vs. outdoors), UV lamp exposure, and frequency of sunscreen use. No association was found between any of these factors and the risk of fMS compared to sMS. On the other hand, engaging in professional outdoor activities or equally indoor and outdoor activities was associated with a reduced risk of MS compared to primarily indoor professional activities. This was the case when comparing fMS with HC and sMS with HC. These findings can be viewed in the context that Serbia covers a relatively small geographical area, with most study participants having spent most of their lives in the country. Therefore, the established effect of latitude on vitamin D synthesis and subsequent risk of MS should not be as pronounced in this environment (Simpson et al., 2019).

Regarding food rich in vitamin D, it was found that seafood consumption in teenage years reduces the risk of fMS compared to sMS (adjusted OR 0.50, 0.26-0.95), while fresh fish consumption was shown to be a protective factor for fMS compared to HC, and trout consumption was associated with a reduced risk of fMS and sMS compared to HC. Fish oil use at ages 13-19 was shown to be a protective factor for sMS compared to HC but not for fMS. Findings on the consumption of fresh fish, seafood, and fish oil associated with reduced MS risk have been observed in several studies (Abdollahpour et al., 2021; Bäärnhielm, Olsson, and Alfredsson, 2014; Black et al., 2020; Cortese et al., 2015; Hoare et al., 2016; Langer-Gould et al., 2020). The finding about seafood consumption in teenage years contributing to the reduction of fMS risk compared to sMS, although intriguing, should be interpreted with caution, as the number of participants who consumed seafood in any group was low, given that seafood consumption is uncommon in Serbia, a landlocked country.

Interestingly, frequent bottled water use at ages 13-19 was associated with an increased risk of fMS and sMS compared to HC. To our knowledge, no study has reported this association so far. Regarding other neurological diseases, aluminum found in bottled water has been linked to an increased risk of dementia (Rondeau et al., 2008). This association is an intriguing finding that requires further investigation in other populations.

Perhaps the most significant finding of this study is that exclusive breastfeeding for more than six months in childhood reduces the risk of fMS in adulthood compared to sMS. Leading organizations such as the World Health Organization and UNICEF recommend exclusive breastfeeding for the first six months of life (World Health Organization, 2021). The implication of this finding is that it might be beneficial for mothers of children with a family history of MS to extend this period, as exclusive breastfeeding for 7-9 months and over 10 months were found to be protective factors for fMS compared to sMS.

Breastfeeding has been shown to reduce the risk of various autoimmune diseases (Diamanti, Capriati, and Bizzarri, 2016; Patelarou et al., 2012; Vieira Borba, Sharif, and Shoenfeld, 2017). This also applies to MS (Alkhawajah et al., 2021; Brenton et al., 2017; Conradi et al., 2013; Hedström et al., 2020a; Holz et al., 2022). However, this study is the first to investigate this association in fMS as an entity separate from sporadic cases (Jovanović et al., 2024). The authors of a multicenter study using the same questionnaire noted that breastfeeding for four months or longer has a protective effect on the risk of MS (Ragnedda et al., 2015). It is noteworthy that this effect appears to be population-specific as well as gender-specific, with the beneficial effect observed among participants from Italy but not from Norway, and the effect being present only in the male population (Ragnedda et al., 2015). The findings of this study, which separates fMS from sMS, also found the association only in the male population (Jovanović et al., 2024). Several mechanisms of the protective effect of breastfeeding on the development of MS have been proposed. These include its components interleukin 10, immunoglobulins, human milk oligosaccharides, which have immunomodulatory properties and a favorable effect on gut microbiota (Atarashi and Honda, 2011; Fernandez et al., 2013; Prioult, Pecquet, and Fliss, 2004).

Although an earlier age of symptom onset among fMS compared to sMS was established in the matched retrospective cohort study (29.9±9.3 vs. 31.3±11.0 years), this association was not statistically significant ($p=0.548$). This is likely due to insufficient study power, considering that findings from the prevalence study conducted on a population registry basis

indicate an earlier age of symptom onset in the fMS group compared to the sMS group. Participants in the retrospective cohort study were matched concerning MS phenotype, with 90% relapsing MS and 10% PPMS. The age at diagnosis (33.7±10.2 in fMS vs. 35.1±11.5 years in sMS) was also lower in fMS but not statistically significant, while the delay in diagnosis (3.7±5.7 in fMS vs. 3.8±6.0 years in sMS) and disease duration were almost identical in the two cohorts (10.4±8.9 in fMS vs. 10.5±9.6 years in sMS). There was also no significant difference in disease progression between the fMS and sMS cohorts measured by MSSS or progression index. Although matching by disease phenotype has its advantages in eliminating the impact of this factor on prognosis, the disadvantage is that it is not possible to test the effect of the difference in familial and sporadic MS occurrence on the disease phenotype. A larger study conducted only in families with first-degree MS relatives showed that familial occurrence of MS increases the risk of progressive disease course (Hensiek et al., 2007). However, no difference in prognosis was found in this study (Hensiek et al., 2007). Similarly, another study found an increased rate of progression in fMS compared to sMS and a slightly earlier onset of the disease, which was statistically significant due to the sample size (29.01 in fMS compared to 29.44 years in sMS, p=0.049) (Wellek et al., 2011). On the other hand, a study conducted in Spain found no difference in the age of disease onset between fMS and sMS (Regal et al., 2018). Due to the nature of MS, determining the exact age of disease onset can sometimes be challenging, as not all patients seek medical attention after the first disease attack, depending on its severity and symptomatology. Since awareness of familial risk in the second and subsequent cases of MS in families leads to earlier diagnosis, using the age at diagnosis is not an adequate solution. More sophisticated efforts are needed to further clarify the specific clinical profile of fMS.

Nine rare or unusual gene variants predicted to be pathogenic with a CADD score greater than 20 were found in this study. Of these nine, five rare variants (all with a gnomADe allele frequency <1%): CLEC16A chr16:11126134_G/A, ALPK2 chr18:58523972_G/T, TYK2 chr19:10378250_C/T, SLC9B1 chr4:102932166_T/C, and WWOX chr16:78115103_C/T, were found exclusively in fMS patients. Some of these variants have previously been associated with MS, while others are new findings in this study. Recent GWAS studies have identified 32 genetic variants in the HLA region and an additional 201 variants outside the HLA region that are associated with MS (International Multiple Sclerosis Genetics Consortium, 2019). These findings account for about 48% of the genetic predisposition for MS, suggesting that a significant portion of genetic susceptibility results from unusual and

rare variants (MAF between 1-5% and less than 1%, respectively). A significant burden of rare risk variants was observed in fMS patients compared to sMS (Everest et al., 2022).

E) Published Papers that are Part of the Doctoral Dissertation

1. Jovanovic, A., Pekmezovic, T., Mesaros, S., Novakovic, I., Peterlin, B., Veselinovic, N., Tamas, O., Ivanovic, J., Maric, G., Andabaka, M., Momcilovic, N., Drulovic, J. Exclusive breastfeeding may be a protective factor in individuals with familial multiple sclerosis. A population registry-based case-control study. Multiple Scler Relat Dis, 2024;82:105392. https://doi.org/10.1016/j.msard.2023.105392 **M22, IF 4.0**

2. Jovanovic, A., Pekmezovic, T., Mesaros, S., Novakovic, I., Peterlin, B., Veselinovic, N., Tamas, O., Ivanovic, J., Maric, G., Andabaka, M., Momcilovic, N., & Drulovic, J.). Earlier age of symptom onset in younger generation of familial cases of multiple sclerosis. Neurol Sci 2024, doi: 10.1007/s10072-024-07512-w. **M22, IF 3.3**

3. Jovanovic, A., Pekmezovic, T., Mesaros, S., Novakovic, I. Significance of interactions between genetic and environmental factors in etiology of multiple sclerosis. Medicinski podmladak, 2025;76:3. doi: 10.5937/mp76-46939 **M53**

F) Conclusion (explanation of scientific contribution)

The doctoral dissertation "Investigation of the prevalence, epidemiological and clinical characteristics of familial occurrence of multiple sclerosis in the population of Belgrade" by Dr. Aleksa Jovanović, as the first of its kind in our population, represents an original scientific contribution to understanding the prevalence of fMS, risk factors for its onset, and the burden of rare gene variants among these patients.

This study aimed to assess various epidemiological, clinical, and genetic aspects of fMS. It was found that the prevalence of fMS in the Belgrade region is 6.4%, and it was similar in both men and women. Sisters were the relatives of patients with fMS with the highest prevalence of MS, followed by mothers and daughters, while the lowest prevalence was found in grandfathers. The prevalence of fMS was higher among female relatives across all categories compared to male relatives.

When assessing the risk factor profiles of patients with fMS compared to sMS, it was shown that the use of cow's milk and powdered milk in childhood increases the risk of fMS compared to sMS. On the other hand, exclusive breastfeeding stood out as a protective factor for fMS compared to sMS, as well as seafood consumption during teenage years.

Compared to HC, the risk of fMS is increased in cases of a positive history of mononucleosis, as well as in individuals who used bottled water as their primary water source at ages 13-19. Conversely, engaging in professional activities outdoors at ages 21-30, consuming fresh fish and trout were identified as protective factors for the onset of fMS compared to HC.

Using whole-exome sequencing, nine rare gene variants predicted to be pathogenic were found among patients with fMS. Two of them were stop-gain mutations with a high predicted impact on gene function, while seven were missense mutations with a moderate predicted impact on gene function. Although the analysis did not show statistically significant enrichment of these variants in the fMS group after FDR correction, it was found that five rare variants were present exclusively in patients with fMS and not in the control group.

This doctoral dissertation was conducted according to all principles of scientific research. The objectives were precisely defined, the scientific approach was original and carefully chosen, and the methodology was contemporary. The results were clearly and systematically presented and discussed, and appropriate conclusions were drawn from them.

Based on all the above, and considering the candidate's previous scientific work, the committee proposes to the Teaching Scientific Council of the Faculty of Medicine, University of Belgrade, to accept the PhD thesis of Dr. Aleksa Jovanović and approve its public defense for the attainment of the academic title of Doctor (PhD) of Medical Sciences.

Belgrade, June 6, 2024

Members of the Committee:

Jelena Drulović, MD, PhD

Gorica Marić, MD, PhD

Borut Peterlin, MD, PhD

Mentor:

Tatjana Pekmezović, MD, PhD

Co-mentors:

Šarlota Mesaroš, MD, PhD

Ivana Novaković, MD, PhD