



Clinical and diagnostic features of patients with familial multiple sclerosis

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ABSTRACT

Background: Multiple Sclerosis (MS) is a demyelinating CNS disease. Most MS cases are sporadic, however about 20 percent of them are hereditary (Ramagopalan and Sadovnick, 2011). The incidence of familial MS is greater in regions with the highest prevalence of this disease (in North America, Europe) (Ramagopalan and Sadovnick, 2011). It is still unclear whether heredity affects the progression and severity of the disease. The aim of this study is to assess the effect of heredity on the development of multiple sclerosis and on the course of disease by analyzing the results of disability and severity scales, as well as clinical studies, and comparing them with sporadic cases.

Methods: Our study included 104 patients with MS. The study group was comprised of 38 patients with history of first degree relative also affected by MS; the control group consisted of 66 patients with no family history (sporadic case). The anonymous survey included questions about demographic and clinical characteristics. Diagnostic results of magnetic resonance imaging (MRI), oligoclonal bands (OCBs) and visual evoked potentials (VEP) were evaluated retrospectively from medical records. Disability assessment was made according to expanded disability status scale (EDSS). Multiple Sclerosis Severity Score (MSSS) score was calculated using conversion table based on EDSS score and duration of disease in years.

Results: MS patients with first degree relative affected by MS tend to have slower onset of the disease, while control group is more likely to have an acute onset ($p < 0.001$). The majority of MS with family history considered that their disease is caused by certain factors, while patients in the control group considered that the disease started without any identifiable cause ($p < 0.05$). Study group more often complained of pyramidal disorders (74% vs. 50%), symptoms related to brainstem (68% vs. 20%) and cortical lesions (47% vs. 20%), headache (37% vs. 9%), back pain (32% vs. 9%) than those in control group, $p < 0.05$. The degree of disability according to EDSS and MSSS scores were higher in the group of patients with first degree relative with MS ($p < 0.05$). The number of exacerbations per year was also higher in study group than in the control group (1.4 vs. 0.8; $p < 0.05$). Patients with a family history have a higher incidence of MRI changes in brainstem (74% vs. 30%) and cerebellum (58% vs. 30%) than the control group ($p < 0.01$).

Conclusions: MS patients with a family history of MS tend to have slower onset of the disease, while control group is more likely to have an acute onset. Patients with a family history of MS more often complained of brainstem and cortical dysfunction, and pain in head or back. Both the degree of disability according to EDSS and MSSS scores were higher in familial cases. They also have a higher number of exacerbations per year. Patients with a history of first degree relative with MS have a higher incidence of MRI changes in brainstem and cerebellum.

Background

Multiple sclerosis (MS) is a chronic demyelinating CNS disease. Abnormalities caused by this disorder disrupt the spread of the nerve impulse and manifest in a variety of neurological symptoms [1,3], such as double vision, blindness of one eye, muscle weakness, sensory or coordination disorders [2]. Due to uncontrolled deterioration of the

nervous system, patients become disabled and incapacitated. Their mobility is impaired and leads to a need for constant care [1].

Most MS cases are sporadic, however about 20 percent of them are hereditary [2]. Although the etiology of the disease is not entirely clear, genetic factors are undoubtedly important. An association between MS and HLA-DR2 allele which belongs to the major histocompatibility complex (MHC) has been identified [4,5]. However, the MHC can be

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only considered to be a cause in 17–62 percent of genetically determined MS cases. Studies with familial disease cases have shown that HLA-DR2 is only found in some patients. Thus, there are other genetic factors that determine heterogeneity of inheritance [4]. HLA-DRB 15 is most commonly detected among Lithuanian patients with MS and plays an important role in susceptibility of disease [6].

Incidence of familial MS is greater in regions with the highest prevalence of this disease (in North America, Europe) [2], and lower where the prevalence is low (in Asia) [7–9]. Familial cases are more common between first and second degree relatives. The relative risk of developing MS has been found to be 9.2 if the first degree relative has MS, and 3.2 or 2.9 if the second or third degree relative suffers from MS, respectively. The smallest number of such cases is found between father and son or mother and son [10]. Hereditary MS cases are more common among twins, especially between sisters. According to studies, if one of the twins is diagnosed with MS, the risk for second twin to develop MS is up to 4.7 percent. This risk is a 31 times higher compared to the general population [11]. A higher incidence of familial cases among sisters can be attributed to a higher incidence of MS in women.

It is still unclear whether heredity affects the progression and severity of the disease. It has been established that age of onset is similar between sporadic and familial cases, and that the course of the disease between twins is similar. However, there is insufficient data to determine whether the course of familial MS is different from sporadic. Several studies have noted that heredity increases the likelihood of disease progression, but does not affect the severity of the disease itself [22]. The aim of this study is to assess the effect of heredity on the development of multiple sclerosis and on the course of disease by analyzing the results of disability and severity scales, as well as clinical studies, and comparing them with sporadic cases.

Materials and methods

Study design

The study was conducted at the Neurology Clinic of the Lithuanian University of Health Sciences Hospital Kaunas Clinics (LSMU Hospital KK). The study was approved by LSMU Ethics Committee for Biomedical Research (No. BEC-MF-158, 2017-12-22). Our study included 104 patients with MS, who were referred to the department of neurology at the Hospital of Lithuanian University of Health Sciences in Kaunas from 22 December 2017 to 28 February 2019 and were willing to participate in the study. The study group was comprised of 38 patients with history of first degree relative also affected by MS and control group consisted of 66 patients without family history of MS (sporadic cases). Criteria for inclusion in the study group: age of patients from 18 to 65 years; diagnosis of MS was confirmed with McDonald criteria; positive history of first degree relative with MS; gave a consent to participate in the research. The results of the study group were compared with the results of the control group which had the same inclusion criteria except for the family history. At first we recruited patients with the family history of MS and analyzed their demographic characteristics, such as gender, age and duration of disease. Controls were admitted inconsecutively in order to match the main study group.

The anonymous survey included questions about demographic and clinical characteristics. Demographic (gender, age, existing co-morbidities and allergies, previous injuries, infectious diseases, vaccinations, pregnancy and history of childbirth for women etc.) and clinical (family history of MS, the duration of the illness, the date of onset, course and type of disease, aggravating factors, current and early symptoms, frequency of exacerbation etc.) data along with the findings of all paraclinical tests were recorded for all the patients. Disability was evaluated using the Kurtzke Expanded Disability Status Scale (EDSS) during the study period and compared with the score which was obtained at the time of diagnosis. Multiple sclerosis severity score (MSSS)

was calculated using conversion table based on EDSS score and duration of disease in years.

Diagnostic results of magnetic resonance imaging (MRI), oligoclonal bands (OCBs) and visual evoked potentials (VEPs) were evaluated retrospectively from medical records. Lumbar puncture and cerebrospinal fluid examination were obtained at the time when disease was first detected. OCBs were defined as positive if more than two bands were present in the cerebrospinal fluid, but absent in the corresponding blood serum. The registration of standard pattern-shift VEPs was done by the Evoked Potential Navigating System (Bio-Logic System Corp., USA). The responses were considered abnormal if the P100 latency was longer than 114 ms (i.e., 2 SD above the mean). All imaging studies were conducted with a 1.5-T MR scanner (MAGNETOM Avanto, Siemens, Erlangen, Germany) with a standard head coil. The locations of MS lesions in MRI were analyzed in the first scan (usually at the time when disease was diagnosed) and the last scan (during study period). Descriptions of two MRI images were reviewed and compared retrospectively from the medical records of the patients, and the conclusion about the dynamics of lesions in MRI was made. There were three categories of MRI dynamics: positive (decreasing activity of lesions), negative (increasing activity of lesions), or no dynamics (activity and localization of lesions were similar in both images).

Multiple sclerosis severity score (MSSS)

MSSS (Multiple Sclerosis Severity Score) is a supplemental scale to EDSS, adding a factor of disease duration to an EDSS score. This gives a derived score that better reflects the severity of the disease and has a better prognostic value. Thus, the severity of the MS in patients with the same EDSS score will depend on the duration of their disease. Higher MSSS score will accordingly reflect a shorter duration of the disease and, at the same time, a more severe course and faster progression. The MSSS score is derived from the conversion table (Fig. 1) using the most recent EDSS score and duration of disease.

Statistical analysis of data

Analysis of the collected data was performed using the statistical package SPSS version 25.0. The mean values that are distributed in the population by Gauss (tested by Shapiro-Wilk test) were compared using the Student-*T* test. Quantitative variables that did not meet the normality criterion were compared using the Mann-Whitney *U* test. Chi-Square Test of Independence was used for statistical analysis of qualitative features. For the control of type I error, the level of significance was selected to be $\alpha = 0.05$. Values of *p* lower than 0.05 ($p < \alpha$) were considered to indicate statistical significance.

Results

The study consisted of 104 patients with MS. The study group was comprised of 38 patients with history of first degree relative also affected by MS: 13 men and 25 women. The control group consisted of 66 patients without family history of MS (sporadic cases): 17 men and 49 women. Both groups did not differ by gender or age ($p > 0.05$). The duration of disease in the study group was 14.34 ± 3.76 years, while in the control group – 15.14 ± 8.46 years ($p > 0.05$). The age of the onset of the disease was similar in both groups ($p > 0.05$). Patients with MS relative tended to have slower onset of the disease, while control group was more likely to have an acute onset ($p < 0.001$). The majority of MS patients with family history considered that their disease is caused by certain factors: childbirth (24%), mental trauma or stress (21%), infectious diseases (11%), head or spinal trauma (8%); meanwhile 71% of patients in the control group considered that the disease started without any identifiable cause ($p < 0.05$). MS patients with family history tended to have relapsing - remitting (42%) or secondary progressive (42%) types of disease; meanwhile most frequent

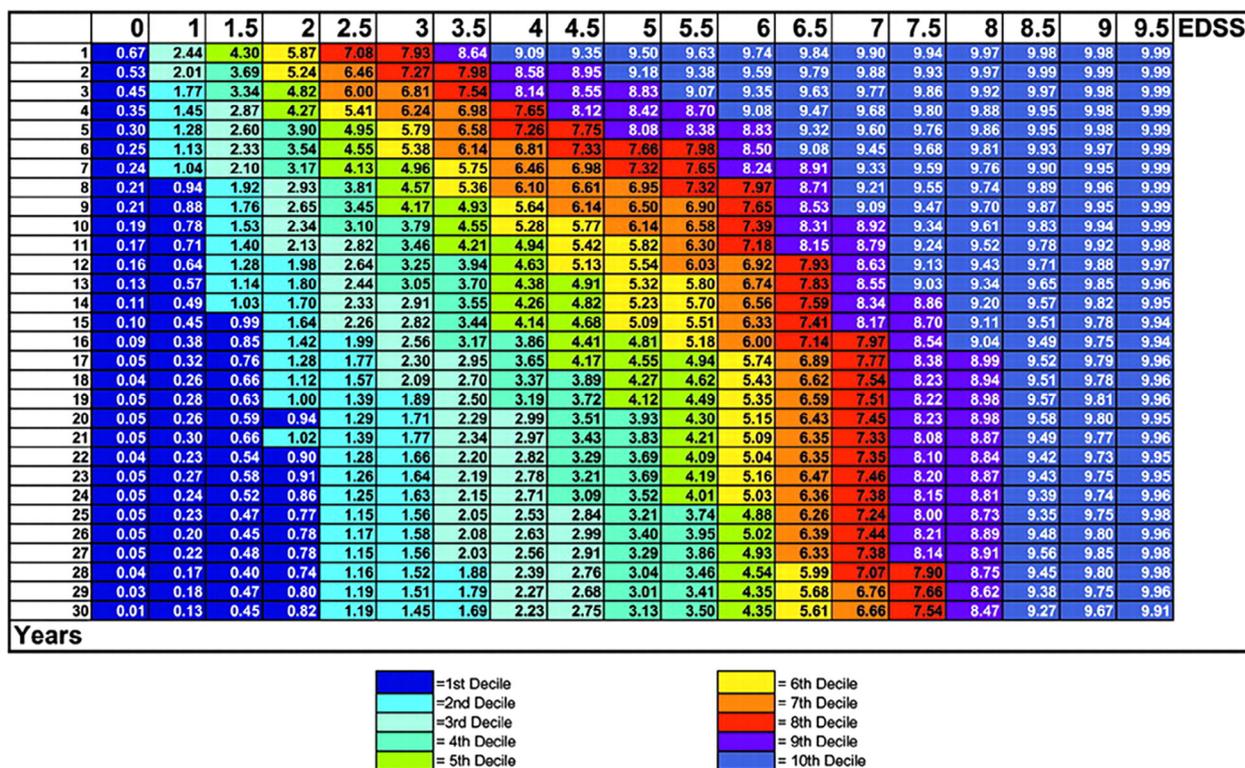


Fig. 1. Source [12]: Multiple Sclerosis Severity Score: using disability and disease duration to rate disease severity. Neurology. 2005 Apr 12;64(7):1144-51.

Table 1

Comparison of clinical characteristics of MS cases with and without a first degree relative with MS.

Clinical characteristics	Study group (N = 38)	Control group (N = 66)	P value
Duration of MS, yr (SD)	14.34 (3.76)	15.14 (8.46)	0.512
Age of onset, yr (SD)	28.89 (7.263)	31.05 (9.515)	0.199
The onset of the disease			
Acute, %	39.5	78.8	0.000
Chronic, %	60.5	21.2	
Subjective cause of disease			
Childbirth, %	23.7	4.5	0.003
Vaccinations, %	5.3	1.5	0.271
Infectious diseases, %	11	10	0.091
Psychological trauma, stress, %	21.1	7.6	0.045
Head or spinal trauma, %	7.9	0	0.021
No subjective cause, %	10.5	71.2	0.000
Type of disease			
Relapsing – remitting, %	42.1	78.8	0.001
Primary progressive, %	15.8	4.5	
Secondary progressive, %	42.1	16.7	

type in control group was relapsing- remitting (79%), $p = 0.001$. Mother was the most frequent first degree relative in familial cases (84%), although no significant relationship between the gender of the participant and his/her family member was found, $p > 0.05$ (Table 1).

At the beginning of the disease, MS patients with a first degree relative more often complained of symptoms related to pyramidal (74% vs. 50%, $p = 0.018$) and brainstem (68% vs. 20%, $p = 0.001$) lesions. They also more commonly had symptoms of cognitive dysfunction (47% vs. 20%, $p = 0.003$), headache (37% vs. 9% $p = 0.001$), back pain (32% vs. 9%, $p = 0.004$) compared to control group. Moreover, current symptoms of head and back pain, cerebral and brainstem dysfunctions were more frequently reported by MS patients with a family history of MS than those who did not have a family history, $p < 0.05$.

Table 2

Comparison of clinical symptoms in cases with and without a first degree relative with MS.

MS symptoms	Study group (N = 38)	Control group (N = 66)	P value
Symptoms at the time of diagnosis			
Sensory s., N (%)	15 (39.5)	32 (48.5)	0.374
Pyramidal s., N (%)	28 (73.7)	33 (50)	0.018
Cerebellum s., N (%)	19 (42.3)	25 (37.9)	0.228
Brainstem s., N (%)	26 (68.4)	13 (19.7)	0.001
Vision s., N (%)	21 (55.3)	30 (45.5)	0.335
Dizziness, N (%)	20 (52.6)	23 (34.8)	0.076
Pelvic organ dysfunction, N (%)	10 (26.3)	12 (18.2)	0.328
Cognitive s., N (%)	18 (47.4)	13 (19.7)	0.003
Weakness/Fatigue, N (%)	20 (52.6)	26 (39.4)	0.191
Headache, N (%)	14 (36.8)	6 (9.1)	0.001
Back Pain, N (%)	12 (31.6)	6 (9.1)	0.004
Current symptoms			
Sensory s., N (%)	18 (47.4)	36 (54.5)	0.481
Pyramidal s, N (%)	18 (47.4)	38 (57.6)	0.315
Cerebellum s, N (%)	14 (36.8)	33 (50)	0.194
Brainstem s., N (%)	19 (50)	12 (18.2)	0.001
Vision s., N (%)	21 (55.3)	28 (42.4)	0.207
Pelvic organ dysfunction, N (%)	6 (15.8)	17 (25.8)	0.238
Cognitive (cerebral) s., N (%)	11 (28.9)	12 (18.2)	0.203
Weakness/Fatigue, N (%)	15 (39.5)	32 (48.5)	0.374
Headache, N (%)	11 (28.9)	7 (10.6)	0.017
Back Pain, N (%)	9 (23.7)	5 (7.6)	0.020
Total number of different CNS systems affected			
Median (min-max)	2 (1–5)	3 (0–7)	0.820

The total number of different CNS systems affected by MS did not differ significantly between the groups (Table 2).

The degree of disability according to EDSS was evaluated twice: at the time of diagnosis and at the last visit (most recent). Both scores were higher in the group of patients with family history of MS,

Table 3
Comparison of the degree of disability in cases with and without a first degree relative with MS.

EDSS Score	MS group with family history	MS group without family history	P value
EDSS score at the time of diagnosis, median (min-max)	1.5 (0–3)	1 (0–3)	0.001
EDSS score at last visit, median (min-max)	5.5 (1.5–8.5)	4 (1–8.5)	0.026

EDSS – expanded disability status score.

Table 4
Comparison of the number of exacerbations in cases with and without a first degree relative with MS.

		Study group	Control group	P value
Number of exacerbations per year	0	N (%) 5 (13.2)	26 (39.4)	< 0.001
	1	N (%) 14 (36.8)	32 (48.5)	
	2	N (%) 17 (44.7)	6 (9.1)	
	3	N (%) 2 (5.3)	2 (3.0)	

$p < 0.05$ (Table 3). Only the most recent EDSS score was used to calculate MSSS, which was also higher in familial cases (5.35 vs. 3.81), $p = 0.047$.

The number of exacerbations per year was higher in familial cases than in the control group (1.4 vs. 0.8; $p < 0.05$). Meanwhile, the control group more often did not experience a single exacerbation in a year, $p < 0.05$ (Table 4).

Patients with a family history of MS had a higher incidence of MRI changes in brainstem (74% vs. 30%) and cerebellum (58% vs. 30%) than the control group ($p < 0.01$). More than half (57.9–74.2%) of patients in both groups had no dynamics of MRI changes, while negative dynamics were observed in 39.5% of familial cases and 24.2% of controls ($p > 0.05$). Only 1.5 – 2.6% of patients in both groups had positive MRI dynamics. VEP abnormalities were observed in 60% of participants, but no difference between the groups was found ($p > 0.05$). OCBs were detected at a similar frequency of 40% in both groups, $p > 0.05$ (Table 5).

Discussion

Our study revealed that majority of MS patients with family history of MS considered their disease to be caused by certain factors. 21% of patients indicated stress as a potential trigger for disease onset. Stress is considered to be one of the risk factors for the development of MS

Table 5
Results of diagnostic tests in cases with and without a first degree relative with MS.

Diagnostic tests	Study group (N = 38)	Control group (N = 66)	P value
Changes in MRI (active/inactive white matter lesions)			
Periventricular, N (%)	38 (100)	64 (97)	0.279
Corpus callosum, N (%)	34 (89.5)	61 (92.4)	0.606
Brainstem, N (%)	28 (73.7)	20 (30.3)	0.000
Cerebellum, N (%)	22 (57.9)	20 (30.3)	0.006
Juxtacortical/subcortical, N (%)	2 (5.3)	2 (3)	0.569
Cervical spinal cord, N (%)	6 (15.8)	13 (19.7)	0.619
Thoracic, lumbar or sacral part of spinal cord, N (%)	2 (5.3)	5 (7.6)	0.65
MRI positive dynamics, N (%)	1 (2.6)	1 (1.5)	0.226
MRI negative dynamics, N (%)	15 (39.5)	16 (24.2)	
MRI without dynamics, N (%)	22 (57.9)	49 (74.2)	
VEP abnormalities, N (%)	23 (60.5)	38 (57.6)	0.107
OCBs - Positive (+), N (%)	29 (43.9)	15 (39.5)	0.079
OCBs - Negative (-), N (%)	16 (42.1)	15 (22.7)	

VEP – visual evoked potential, MRI – magnetic resonance imaging, OGBs – oligoclonal bands.

because it leads to changes in the hypothalamic-pituitary-adrenal axis [15]. 24% of women with first degree relative with MS thought that the birth of child could trigger the onset of the disease. According to some authors, hormonal changes occurring during pregnancy can affect the onset and remission of MS in already ill women [16]. In addition, one of the predisposing factors for MS may be infectious disease [17]. When considering the types of disease, the prevalence of relapsing-remitting (RR) and secondary progressive types were equally common in familial cases, while RR was the most common type in the control group. According to other studies, the most frequent type of MS is RR (85%) [18]. Our study confirms it, because the majority of patients with MS were diagnosed with RR type. However, it is obvious that patients with a family history of MS are also characterized by frequent secondary progression (SP). These are mostly the patients who progressed from RR type to SP. Moreover, we found that the most frequent first degree relative with MS was a mother. Metanalysis found that the risk of having a child with MS depends on the sex of the diseased parent [8–14]. Many studies have found that the risk increases with an affected mother [8,13,14].

Our study revealed that the number of exacerbations per year was higher in familial cases than in the control group (1.4 vs. 0.8). Rate of exacerbations is higher in the first year of disease and gradually decreases [18]. Some studies suggest that the higher frequency of exacerbations in the first five years of the disease is associated with an increased risk of developing SP type and disability [19]. Exacerbations are more common after stressful experiences [20]. Since the cause of the exacerbations is usually subjective, there are no reliable results that could allow us to determine association between exacerbations and external factors. Disability caused by MS is assessed by EDSS. The disability score was higher in the group of familial cases. EDSS is often used not only in clinical practice but also in various scientific researches. However, this scale also has some disadvantages. A score greater than 4 depends mainly on the ability to walk. In addition, developing dementia, loss of vision or hand weakness remain underestimated. Also, a higher score does not always affect the patient's quality of life, some symptoms may be transient or only visible to the examiner. Moreover, MSSS score values were also higher in the group of patients with family history of MS. They tend to have a more severe and more progressive form of the disease. Thus, it can be assumed that heredity affects the progression and prognosis of the disease.

MRI is one of the main studies to confirm MS diagnosis [21]. Patients with a family history of MS were more likely to have lesions in brainstem, cerebellum. In both groups, the dynamics of MRI changes were mostly not observed. VEP study showed changes in 60% of patients overall. This confirms the data of metanalysis (40–100%). Although VEP prolongation is one of the diagnostic criteria of MS, it can be found due to other causes such as older age, decreased ability to focus, drowsiness, vitamin B12 deficiency or nerve compression [21].

On the other hand, our study was limited to the relatively small patient cohort and therefore should be considered as a pilot study. Our results awaiting to be reconfirmed on the larger set of Lithuanian MS patients in the near future.

Conclusions

Patients with familial MS tend to have slower onset of the disease, while those without first degree relative are more likely to have an

acute onset. The majority familial cases considered that their disease is caused by certain factors, while patients in the control group considered that the disease started without any identifiable cause. MS patients with family history of MS tend to have recurrent – remitting or secondary progressive types of disease. Meanwhile most frequent type in control group is recurrent – remitting. Patients with a family history of MS more often complained of brainstem and cortical dysfunction, and pain in head or back. Both the degree of disability according to EDSS and MSSS score were higher in familial cases. Moreover, they also have a higher number of exacerbations per year. That means familial cases tend to have a more severe and progressive form of the disease. Patients with a history of a first degree relative have a higher incidence of MRI changes in brainstem and cerebellum.

Declarations

Ethics approval and consent to participate

The study was approved by LSMU Ethics Committee for Biomedical Research (No. BEC-MF-158, 2017-12-22). All patients provided written informed consent to participate. A copy of the written consent is available for review by the Editor of this journal.

Availability of data and materials

The dataset generated and analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

DA collected and analyzed data, drafted the manuscript and carried out the literature search. RB, IK participated in the acquisition and interpretation of data. RB, AV made contributions to supervision in data collection and management and revising the manuscript. All authors read and approved the final manuscript, and agreed to be accountable for all aspects of the work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2019.109310>.

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