Clinical Features of Patients With Familiar Multiple Sclerosis in Lithuania

CURRENT STATUS: POSTED

Denas Andrijauskis
Lietuvos sveikatos mokslu universitetas Medicinos fakultetas
andr.denas@gmail.com Corresponding Author

Renata Balnyte
Lietuvos sveikatos mokslu universitetas Medicinos akademija

Ieva Keturkaite
Lietuvos sveikatos mokslu universitetas Medicinos fakultetas

Antanas Vaitkus
Lietuvos sveikatos mokslu universitetas Medicinos fakultetas

DOI:
10.21203/rs.2.9297/v1

SUBJECT AREAS
Internal Medicine Specialties

KEYWORDS
multiple sclerosis, familiar cases, MRI, MSSS, EDSS
Abstract
Background. Most multiple sclerosis (MS) cases are sporadic, however about 20 percent are hereditary. 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, severity scales and 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 family history of MS; the control group consisted of 66 patients with no family history. The survey included questions about demographic and clinical characteristics. Diagnostic results were evaluated retrospectively from medical records. Disability assessment was made according to EDSS. MSSS score was calculated using conversion table. Results. Patients with a family history tend to have slower onset of the disease, while control group is more likely to have an acute onset (p <0.001). Study group more often complained of symptoms related to pyramidal (74 % vs. 50 %) and brainstem (68 % vs. 20 %), cognitive dysfunction (47 % vs. 20 %), headache (37 % vs. 9 %), back pain (32 % vs. 9 %) than those in control group, p <0.05. EDSS and MSSS scores were higher in familiar cases (p <0.05). The number of exacerbations per year was also higher in study 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. Patients with a family history 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 EDSS and MSSS scores were higher in familiar cases. They also have a higher number of exacerbations per year. Patients with a family history 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 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 belonging to the main human cohesive compatibility complex (MHC) has been identified [4, 5]. However, according to preliminary estimates, the MHC can be only considered a cause in 17-62 percent of genetically determined MS cases. Studies with familiar 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 familiar 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]. Familiar 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 [10]. Hereditary MS cases are more common among twins, especially between sisters. The smallest number of such cases is found between father and son or mother and son. According to studies, the risk of getting a second twin with MS is up to 4.7 percent, and this is a 31 times higher risk compared to the general population [11]. A higher incidence of familiar 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 between sporadic and familiar cases is similar, and that the course of the disease between twins is similar. However, there is insufficient data to determine whether the course of hereditary disease 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.

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, severity scales and clinical studies, and comparing them with sporadic cases.

Materials And Methods
2.1 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. Criteria for inclusion in the study group: patients aged 18 to 65 years; diagnosis of MS is confirmed with McDonald criteria; positive or negative family history of MS (MS first-line relative); received an appropriate course of treatment with disease modifying drugs; consent to participate in the investigation). The study group was comprised of 38 patients with family history of MS and control group consisted of 66 patients without family history of MS (sporadic cases). 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.

Demographic (gender, age, existing co-morbidities and allergies, previous injuries, infectious diseases, vaccinations, pregnancy and history of childbirth for women etc.) and clinical data (family history of MS, the duration of the illness, the date of onset, course, potentially aggravating factors, current and early symptoms, frequency of exacerbation etc.), the findings of all paraclinical tests were recorded for all the patients. Disability was evaluated using the Kurtzke Expanded Disability Status Scale (EDSS). The EDSS was evaluated during the study period and compared to the score at the time of diagnosis. For both groups, MSSS score was calculated using conversion table based on EDSS score and duration of disease in years.

All the laboratory results (oligoclonal bands [OCBs]), MRI results, and data of visual evoked potentials (VEPs) were reviewed retrospectively from the medical records of the patients. 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 CSF, but absent in the corresponding blood serum. The standard pattern-shift VEPs were recorded for all 104 patients. The registration of 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).

2.2 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 itself and has a better prognostic value. Thus, the severity of the disease in patients with the same EDSS score will depend on how long they are sick. 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 (Figure 1) with the EDSS score and disease duration in the year. This scale has not been applied in Lithuania yet.

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

2.3 Evaluation of MRI findings

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 two different scans: the very first scan (usually at time of diagnosis) 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).

2.4 Statistical Analysis of Data

Analysis of the collected data was performed using the statistical package SPSS version 25.0. Comparisons of mean age at onset of MS across groups were carried out using the Student t test. Parametric statistical criteria were used for the normally distributed quantitative variables (estimated with Kolmogorov–Smirnov and Shapiro–Wilk tests) and the mean and standard deviations (SD) were calculated. For the control of type I error, the level of significance was selected to be \( a = 0.05 \). Values of \( p \) lower than 0.05 (\( p < a \)) were considered to indicate statistical significance.
Results
The study consisted of 104 patients with MS. The study group consisted of MS with family history of MS: 13 men and 25 women. The control group consisted of MS without a family history: 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 at the onset of the disease was similar in both groups (p > 0.05). Patients with a family history 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: 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 tend to have relapsing-remitting (42%) or secondary progressive (42%) types of disease; meanwhile most frequent type in control group is relapsing-remitting (79%), p = 0.001). Mother was the most frequent family member with MS in familiar cases (84%), although no significant relationship between the gender of the subject and his/her family member was found (p > 0.05). (Table 1)

Table 1. Comparison of clinical characteristics of patients with multiple sclerosis
| 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                 | 0.000055|
| 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                 |         |

MS patients with a family history at the beginning of the disease (at the time of diagnosis) more often complained of symptoms related to pyramidal (74 % vs. 50 %, p=0.018) and brainstem (68 % vs. 20 %, p=0.001) lesions, 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 than those who did not have a family history, p <0.05 (Table 2).

Table 2. *Comparison of clinical symptoms in patients with multiple sclerosis*
| 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 degree of disability according to EDSS was higher in the group of patients with family history (p <0.05). MSSS scores were higher in study group (5.35 vs. 3.81), p = 0.047 (Table 3).

Table 3. Comparison of the degree of disability in patients with multiple sclerosis
EDSS - expanded disability status score

In the MS patient group family history), the number of exacerbations per year was higher than in the control group (1.4 vs. 0.8; p <0.05). Meanwhile, the control group more often does not experience a single exacerbation in one year, p <0.05 (table 4).

Table 4. *Comparison of the number of exacerbations*

| Number of exacerbations per year | Study group | Control group | P value |
|---------------------------------|-------------|---------------|---------|
| 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)   |

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). 65% of patients in both groups showed no dynamics of MRI changes, while negative and positive dynamics were observed in 32% and 2% of patients, respectively (p > 0.05). VEP prolongation changes was observed in 60% of cases, but no difference between the groups was found (p > 0.05). Oligoclonal bands were detected at a similar frequency in both groups (p > 0.05) (table 5).

Table 5. *Results of diagnostic tests in patients with multiple sclerosis*
### Discussion

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

According to literature, stress is considered to be one of the risk factors for the development of MS because it leads to changes in the hypothalamic-pituitary-adrenal axis [15]. 24% of women with MS in first degree relative thought that the birth of child could trigger the onset of the disease. According to the 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 MS with family history, while RR was the most
common type in the control group. According to literature, 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 overall. However, it is obvious that patients with a family history are also characterized by frequent secondary progression (SP). These are mostly the patients who progressed from RR type to SP. As our study focused on the role of inheritance, each participant revealed if they have a first-degree relative with MS. We found that the most frequent family member of MS participant, who is also affected by 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 in familiar cases was higher 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 in the literature that could allow us to determine association between exacerbations and external factors, such as infection. Disability caused by MS is assessed by EDSS. The disability score was higher in the group of familiar 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 MS with family history. 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 a family history tend to have slower onset of the disease, while control group is more likely to have an acute onset. 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. MS patients with family history 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 familiar cases. Moreover, they also have a higher number of exacerbations per year. That means familiar cases tend to have a more severe and progressive form of the disease. Patients with a family history have a higher incidence of MRI changes in brainstem and cerebellum. The results of VEP and oligoclonal band studies did not differ significantly between the groups.

**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.

**Consent for publication**

Not applicable.

**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.

Funding

The study was supported by the grant from the Research Foundation, Lithuanian University of Health Sciences.

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.

Acknowledgements

Not applicable

References

1. Alonso A, Hernán MA. Temporal trends in the incidence of multiple sclerosis: a systematic review. Neurology 2008; 71:129.

2. Ramagopalan SV, Sadovnick AD. Epidemiology of multiple sclerosis. Neurol Clin 2011; 29:207.

3. Orton SM, Herrera BM, Yee IM, et al. Sex ratio of multiple sclerosis in Canada: a longitudinal study. Lancet Neurol 2006; 5:932.

4. van Luijn MM, Kreft KL, Jongsma ML, et al. Multiple sclerosis-associated CLEC16A controls HLA class II expression via late endosome biogenesis. Brain 2015; 138:1531.

5. da Silva Bernardes, Antão Paiva, Ribeiro Paradela, Papais Alvarenga, Ferreira Pereira, Vasconcelos, Papais Alvarenga. Familial multiple sclerosis in a Brazilian sample: Is HLA-DR15 involved in susceptibility to the disease? J Neuroimmunol. 2019 Feb 23;330:74-80.

6. Balnyte R, Rastenyte D, Vaitkus A, Mickeviciene D, Skrodeniene E, Vitkauskiene A, Uloziene I. The importance of HLA DRB1 gene allele to clinical features and disability in patients with multiple sclerosis in Lithuania. BMC Neurol. 2013 Jul 9;13:77.
7. Heinzlef O, Alamowitch S, Sazdovitch V, et al. Autoimmune diseases in families of French patients with multiple sclerosis. Acta Neurol Scand 2000; 101:36.

8. Nielsen NM, Westergaard T, Rostgaard K, et al. Familial risk of multiple sclerosis: a nationwide cohort study. Am J Epidemiol 2005; 162:774.

9. Goodin DS. The epidemiology of multiple sclerosis: insights to disease pathogenesis. Handb Clin Neurol 2014; 122:231. Koch-Henriksen N, Sørensen PS. The changing demographic pattern of multiple sclerosis epidemiology. Lancet Neurol 2010; 9:520.

10. Herrera BM, Ramagopalan SV, Lincoln MR, et al. Parent-of-origin effects in MS: observations from avuncular pairs. Neurology 2008; 71:799.

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

12. Herrera BM, Ramagopalan SV, Orton S, et al. Parental transmission of MS in a population-based Canadian cohort. Neurology 2007; 69:1208.

13. Hoppenbrouwers IA, Liu F, Aulchenko YS, et al. Maternal transmission of multiple sclerosis in a dutch population. Arch Neurol 2008; 65:345.

14. Kantarci OH, Spurkland A. Parent of origin in multiple sclerosis: understanding inheritance in complex neurologic diseases. Neurology 2008; 71:786.

15. Chaudhuri A, Behan PO. Fatigue in neurological disorders. Lancet. 2004; 363:978 – 88

16. Bove R, Gilmore W. Hormones and MS: Risk factors, biomarkers, and therapeutic targets. Multiple Sclerosis Journal. 2018; 24(1), 17-21.

17. Melcon MO, Correale J, Melcon CM. Is it time for a new global classification of multiple sclerosis? J Neurol Sci 2014; 344:171-81.

18. Vollmer T. The natural history of relapses in multiple sclerosis. J Neurol Sci 2007; 256 Suppl 1:S5.

19. Eriksson M, Andersen O, Runmarker B. Long-term follow up of patients with clinically isolated syndromes, relapsing-remitting and secondary progressive multiple sclerosis. Mult Scler 2003; 9:260.

20. Mohr DC, Hart SL, Julian L, et al. Association between stressful life events and exacerbation in multiple sclerosis: a meta-analysis. BMJ 2004; 328:731.
21. Palace J. Making the diagnosis of multiple sclerosis. Journal of Neurology, Neurosurgery & Psychiatry. 2001; 71(2), 3-8.

Figures

Figures

|          | 0  | 1   | 1.5 | 2   | 2.5 | 3   | 3.5 | 4   | 4.5 | 5   | 5.5 | 6   | 6.5 | 7   | 7.5 | 8   | 8.5 | 9   | 9.5 | EDSS |
|----------|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| MSSS     |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Score    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Source   | [12]: Multiple Sclerosis Severity Score: using disability and disease duration to rate disease severity. Neurology. 2005 Apr 12;64(7):1144-51.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

Dataset (Additional file 3).xlsx
Survey (Additional file 2).docx