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Associations between Infections and Clinical Features of Multiple Sclerosis: An Exploratory, Cross-Sectional Study Based on Self-Reported Infection History in a Lithuanian Cohort

Naglis Vičkačka*
Faculty of Medicine, Lithuanian University of Health Sciences, Kaunas, Lithuania
E-mail: naglis.vickacka@stud.lsmu.lt
ORCID ID https://orcid.org/0009-0006-5792-9816

Revaldė Vasiliauskaitė
Faculty of Medicine, Lithuanian University of Health Sciences, Kaunas, Lithuania
E-mail: revalde.vasiliauskaite@stud.lsmu.lt
ORCID ID https://orcid.org/0009-0005-7976-6918

Renata Balnytė
Department of Neurology, Faculty of Medicine, Lithuanian University of Health Sciences, Kaunas, Lithuania
E-mail: renata.balnyte@lsmu.lt
ORCID ID https://orcid.org/0000-0002-8772-6810

Abstract. ***Background:*** Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system, with its etiology being linked to a combination of genetic and environmental factors. Infections, both viral and bacterial, are considered significant environmental triggers that may influence both the development and progression of MS. However, the specific associations between different infectious diseases and the clinical course of MS are not fully elucidated. This study aims to determine the associations between various infections and the development, clinical symptoms, and disability progression in Lithuanian MS patients.

Materials and Methods: A cross-sectional study was conducted at the Outpatient Department of Nervous System Diseases at LSMUL KK Neurology Clinic between January 2024 and January 2025. The study involved 72 patients diagnosed with MS and a control group of 72 individuals without MS. Data were collected by using a structured questionnaire covering demographics, the socioeconomic status, and a retrospective, self-reported lifetime history of specific infectious diseases across childhood, adolescence, and adulthood. This was supplemented by a retrospective analysis of the patients' medical records to obtain clinical data, including the MS course, presenting symptoms, and disability status assessed by the Expanded Disability Status Scale (EDSS). Statistical analysis was performed by using IBM SPSS to compare the two groups.

Results: The mean number of infectious diseases experienced by MS patients (childhood, teenhood, and adulthood) was 2.57 (SD ± 1.31), compared to 2.09 (SD ± 1.07) in the control group, with no significant difference between the groups ($p = 0.101$). The most common illness among MS patients was chickenpox (n = 53; 73.6 %), while the most frequent illness in the control group was COVID-19 (n = 54; 75%). During childhood, control participants had significantly higher rates of acute tonsillitis ($p = 0.029$) and parotitis ($p = 0.049$). In teenhood, control participants were more likely to experience acute tonsillitis ($p < 0.001$), and, in adulthood,

* Corresponding author

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herpes infections ($p = 0.013$) and COVID-19 ($p = 0.009$). MS patients had a significantly higher number of cases of chickenpox in adulthood ($p = 0.016$). MS patients who had experienced acute tonsillitis were more likely to report motor (n = 14; $p = 0.025$) and visual impairments (n = 17; $p = 0.047$). Those who had contracted chickenpox were more likely to have sensory (n = 20; $p = 0.027$) and pelvic organ dysfunctions (n = 17; $p = 0.034$). MS patients who had experienced pneumonia had a higher incidence of brainstem dysfunction (n = 16; $p = 0.005$) and cerebellar dysfunction (n = 18; $p = 0.001$). Herpes infections in MS patients were associated with a higher frequency of visual impairments (n = 11; $p = 0.019$). No statistically significant difference was observed between infections post-MS diagnosis and relapse occurrence ($p > 0.05$). Patients who had pneumonia ($p = 0.012$) and COVID-19 ($p = 0.023$) had significantly lower average EDSS scores compared to those who had not experienced these illnesses.

Conclusions: Our research has found that the most common infection in the MS group was chickenpox, particularly in adulthood. The most common infection in the control group was COVID-19. The control group had a higher incidence of acute tonsillitis and mumps in childhood, acute tonsillitis in adolescence, and *Herpes* infection and COVID-19 in adulthood compared to the MS group. Patients with a history of acute tonsillitis more frequently reported motor and visual impairments; a history of chickenpox was associated with sensory and pelvic organ dysfunction; pneumonia was linked to brainstem and cerebellar dysfunction; and *Herpes* infection was associated with visual impairments. Patients with a history of pneumonia or COVID-19 had a lower mean EDSS score. These findings are exploratory and hypothesis-generating. The observed associations should be interpreted with caution due to the subjective nature of the self-reported exposure data and the lack of statistical adjustment for multiple comparisons.

Keywords: multiple sclerosis, infectious diseases.

Infekcijų ir išsėtinės sklerozės klinikinių požymių sąsaja: skerspjūvio tyrimas, pagrįstas Lietuvos tiriamųjų pačių pateikta infekcijų istorija

Santrauka. ***Įvadas:*** Išsėtinė sklerozė (IS) yra lėtinė centrinės nervų sistemos uždegiminė ir neurodegeneracinė liga, kurios etiologija siejama su genetinių ir aplinkos veiksnių deriniu. Infekcijos – tiek virusinės, tiek bakterinės – yra svarbūs aplinkos veiksniai, galintys daryti įtaką tiek IS atsirasti, tiek jai progresuoti. Tačiau konkretaus įvairių infekcinių ligų ir IS klinikinės eigos ryšio iki galo nėra išaiškinta. Šio tyrimo tikslas – nustatyti Lietuvos IS pacientų įvairių infekcijų ir IS išsivystymo, klinikinių simptomų ir negalios progresavimo sąsajas.

Medžiaga ir metodai: 2024 m. sausio mėn. – 2025 m. sausio mėn. LSMUL KK Neurologijos klinikos Nervų sistemos ligų ambulatoriniame skyriuje buvo atliktas skerspjūvio tyrimas. Tyrime dalyvavo 72 pacientai, kuriems diagnozuota IS, ir 72 asmenų, nesergančių IS, kontrolinė grupė. Duomenys buvo renkami naudojant struktūruotą klausimyną, apimantį pacientų demografinius duomenis, socialinę ir ekonominę padėtį bei retrospektyvią, jų pačių pateiktą konkrečių infekcinių ligų istoriją per visą gyvenimą – vaikystėje, paauglystėje ir suaugus. Tai buvo papildyta retrospektyvia pacientų medicininių įrašų analize, siekiant gauti klinikinius duomenis, įskaitant IS eigą, pasireiškiančius simptomus ir negalios laipsnį, įvertintą pagal išplėstinę negalios laipsnio skalę (EDSS). Statistinė analizė atlikta naudojant „IBM SPSS“ programą, siekiant palyginti abi grupes.

Rezultatai: Vidutinis IS pacientų patirtų infekcinių ligų skaičius (vaikystėje, paauglystėje ir suaugus) buvo 2,57 (SD ± 1,31), palyginti su 2,09 (SD ± 1,07) kontrolinės grupės; reikšmingo skirtumo tarp grupių nebuvo (p = 0,101). Dažniausia liga tarp IS pacientų buvo vėjaraupiai (n = 53; 73,6 %), o kontrolinėje grupėje – COVID-19 (n = 54; 75 %). Vaikystėje kontrolinės grupės dalyviai statistiškai reikšmingai dažniau sirgo ūmiu tonzilitu (p = 0,029) ir parotitu (p = 0,049). Paauglystėje kontrolinės grupės dalyviai dažniau sirgo ūmiu tonzilitu (p < 0,001), o suaugus – herpeso infekcijomis (p = 0,013) ir COVID-19 (p = 0,009). IS pacientai suaugus sirgo vėjaraupiais statistiškai reikšmingai dažniau (p = 0,016). IS pacientai, sirgę ūmiu tonzilitu, dažniau nurodė buvus motorinius (n = 14; p = 0,025) ir regos sutrikimus (n = 17; p = 0,047). Tie, kurie sirgo vėjaraupiais, dažniau turėjo jutimo (n = 20; p = 0,027) ir dubens organų funkcijos sutrikimų (n = 17; p = 0,034). IS pacientai, sirgę plaučių uždegimu, dažniau patyrė smegenų kamieno disfunkciją (n = 16; p = 0,005) ir smegenėlių disfunkciją (n = 18; p = 0,001). Herpeso infekcijos IS pacientams buvo susijusios su dažnesniais regos sutrikimais (n = 11; p = 0,019). Nebuvo pastebėta statistiškai reikšmingo skirtumo tarp infekcijų, patirtų po IS diagnozės, ir atkryčių dažnio (p > 0,05). Pacientų, kurie sirgo plaučių uždegimu (p = 0,012) ir COVID-19 (p = 0,023), buvo statistiškai reikšmingai mažesni vidutiniai EDSS balai, palyginti su tais, kurie šių ligų nebuvo patyrę.

Išvados: Mūsų tyrimas parodė, kad dažniausia IS grupės pacientų infekcija buvo vėjaraupiai, ypač suaugus, o dažniausia kontrolinės grupės dalyvių nurodyta infekcija buvo COVID-19. Kontrolinės grupės, palyginti su IS grupe, buvo didesnis ūmaus tonzilito ir parotito paplitimas vaikystėje, ūmaus tonzilito – paauglystėje, o herpeso infekcijos ir COVID-19 – suaugus. Pacientai, kurių anamnezėje buvo užfiksuotas ūmus tonzilitas, dažniau skundėsi motoriniais ir regos sutrikimais; vėjaraupių anamnezė buvo susijusi su jutimo ir dubens organų disfunkcija; pneumonija – su smegenų kamieno ir smegenėlių disfunkcija; o herpeso infekcija buvo susijusi su regos sutrikimais. Pacientai, kurių anamnezėje buvo užfiksuota pneumonija arba COVID-19, turėjo žemesnį vidutinį EDSS balą. Šie rezultatai yra tiriamojo pobūdžio ir skirti hipotezėms suformuluoti. Nustatytos sąsajos turėtų būti interpretuojamos atsargiai dėl subjektyvaus savarankiškai pateiktų duomenų pobūdžio ir statistinio koregavimo dėl daugkartinių palyginimų trūkumo.

Raktažodžiai: išsėtinė sklerozė, infekcinės ligos.

Introduction

Multiple Sclerosis (MS) is the most common chronic inflammatory, demyelinating, and neurodegenerative disease of the central nervous system among young adults. In the initial stages of the disease, many patients experience reversible symptoms of neurological dysfunction that last for several days or weeks. Over time, irreversible clinical and cognitive impairments emerge [1]. This condition is driven by an autoimmune response, with a pathogenesis involving both genetic and environmental factors. One of the key environmental factors that increases the risk of developing MS is various infectious diseases. Pathogens associated with MS development or exacerbation include various bacteria, such as Chlamydia pneumoniae and H. pylori, and viruses such as Epstein-Barr virus (EBV), human herpesvirus 6 (HHV-6), human endogenous retrovirus (HERV), cytomegalovirus (CMV), and varicella-zoster virus (VZV) [2]. According to the current data, the strongest association between MS development and infectious disease is observed with EBV infection. This viral infection, which can be asymptomatic or cause infectious mononucleosis, significantly increases the risk of MS, and it is therefore believed to be one of the primary causes of the disease [3]. However, to date, no single pathogen has been accepted as the causative agent. Furthermore, frequent infections of the upper respiratory, gastrointestinal, and urogenital tracts may be associated with MS exacerbations. The pathophysiological mechanisms that may link MS and infectious diseases are thought to occur through the ability of microbial antigens to modulate the neuroimmune system in individuals with a susceptible genetic background [2]. By investigating the link between diseases caused by various pathogens and this chronic autoimmune condition, it is possible to better understand the pathogenesis of MS and identify potential prevention methods. Additionally, by identifying specific pathogens associated with disease exacerbations, targeted treatment strategies or various prophylactic measures could be implemented to reduce the disease progression and improve the patients' quality of life. The aim of this exploratory, hypothesis-generating study was to evaluate potential non-causal associations between self-reported infectious diseases and the clinical features of MS, by analyzing the history of infectious diseases in MS patients and a matched control group, and by assessing the MS patients' symptoms and disability according to the *Expanded Disability Status Scale* (EDSS). A study of a similar nature has not yet been conducted in Lithuania.

Materials and Methods

Study design and participants

An exploratory, cross-sectional study was conducted from January 2024 to January 2025 at the Outpatient Department of the Neurology Clinic, Hospital of Lithuanian University of Health Sciences Kaunas Clinics. A total of 72 patients with a confirmed diagnosis of multiple sclerosis (MS) and 72 control group participants were included in the study. The inclusion criteria for the MS group were age ≥ 18 years, a diagnosis of MS based on the 2010 or 2017 McDonald criteria, and voluntary

participation. The control group consisted of age- and sex-matched individuals without a diagnosis of MS or other chronic CNS diseases.

The controls were recruited concurrently as a convenience sample of healthy community volunteers via distributed questionnaires. The criteria for the control group included being ≥ 18 years of age and having no diagnosis of MS or other chronic central nervous system diseases. They were evaluated by using the same structured questionnaire to assess their basic socioeconomic status, focusing on the place of residence (urban vs. rural), educational level, and employment status. While basic socioeconomic factors were assessed, we acknowledge that unmeasured disparities in the overall healthcare utilization, health literacy, and comprehensive vaccination history between the clinical MS cohort and the volunteer control group remain unknown. These unrecorded variables represent a confounding risk, as they directly influence both the true exposure to infectious agents and the individual's ability to recall them accurately. While there were no significant differences in the age, sex, or place of residence between the two groups, the control group had a higher proportion of individuals with higher education and those engaged in physical or mental work, whereas the MS group had higher rates of unemployment and special secondary education. Notably, detailed data regarding general healthcare utilization or a comprehensive vaccination history were not systematically recorded for either group, which is a factor that could have influenced the infection exposure and recall.

The data were collected by using a dual approach: a structured questionnaire administered to all participants, and a retrospective analysis of the outpatient medical records of the MS patients was conducted. The questionnaire gathered information on the demographics, socioeconomic status, and a detailed lifetime history of specific infectious diseases across different life stages (childhood, teenhood, and adulthood). The self-reported history of past infections was based entirely on subjective participant recall, which introduces potential for recall bias and misclassification. The retrospective medical record review provided clinical data for the MS patients, including the disease course, presenting the symptoms, and the disability level, which was assessed by using the *Expanded Disability Status Scale* (EDSS). The *Multiple Sclerosis Severity Score* (MSSS) was determined based on the disability of patients according to the EDSS and the duration of the disease in years.

Statistical analysis

The data were tabulated in *Microsoft Excel*, and statistical analyses were performed by using IBM SPSS Statistics for Windows (Version 29.0). Continuous variables are expressed as mean ± *Standard Deviation* (SD). Categorical variables are presented as the frequency and percentage (%). The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the normality of data distribution. For group comparisons, the Student's t-test was used for normally distributed continuous data, while the Mann-Whitney U test was used for non-normally distributed data. The Chi-square (χ^2) test was used to compare the frequencies of categorical variables. A p-value of < 0.05 was deemed statistically significant. However, due to the exploratory nature of this study, extensive statistical testing was performed without adjustment for multiple comparisons, which means that some significant p values may represent chance findings.

Results

History of Infectious Diseases in MS and Control Groups

The mean number of self-reported lifetime infectious diseases was 2.57 (SD ± 1.31) in the MS patient group and 2.09 (SD ± 1.07) in the control group; this difference was not statistically significant ($p = 0.101$). During childhood, the most common infection in both groups was chickenpox (59.7% in the MS group, 73.6% in the control group). The control group reported a significantly higher

incidence of acute tonsillitis ($p = 0.029$) and mumps ($p = 0.049$). In adolescence, the most common infection in the MS group was *Herpes* infection (18.1%), while in the control group, it was acute tonsillitis (44.4%). The rate of acute tonsillitis was significantly higher in the control group ($p < 0.001$). In adulthood, the most common infection in both groups was COVID-19. The control group had a significantly higher incidence of *Herpes* infection ($p = 0.013$) and COVID-19 ($p = 0.009$), while MS patients reported a significantly higher rate of adult-onset chickenpox (11.1% vs. 1.4%; $p = 0.033$). The distribution of infectious diseases across different life stages is presented in Table 1.

Table 1. Distribution of infectious diseases in multiple sclerosis patients and the control group at different life stages

Infectious diseases	Multiple sclerosis patients (n=72)	Control group (n=72)	*p* value
Childhood (until 12 years)			
Infectious mononucleosis, n (%)	0 (0)	0 (0)	n.s.
Acute tonsillitis, n (%)	25 (34.7)	38 (52.7)	*p*<0.05
Chickenpox, n (%)	43 (59.7)	53 (73.6)	n.s.
Measles, n (%)	4 (5.6)	7 (9.7)	n.s.
Rubella, n (%)	7 (9.7)	9 (12.5)	n.s.
Pneumonia, n (%)	17 (23.6)	25 (34.7)	n.s.
Parotitis n (%)	5 (6.9)	14 (19.4)	*p*<0.05
Herpes infection, n (%)	9 (12.5)	16 (22.2)	n.s.
Toxoplasmosis, n (%)	0 (0)	0 (0)	n.s.
Teenhood (13–17 years)			
Infectious mononucleosis, n (%)	0 (0)	0 (0)	n.s.
Acute tonsillitis, n (%)	12 (16.7)	32 (44.4)	*p*<0.05
Chickenpox, n (%)	8 (11.1)	4 (5.6)	n.s.
Measles, n (%)	0 (0)	0 (0)	n.s.
Rubella, n (%)	0 (0)	1 (1.4)	n.s.
Pneumonia, n (%)	6 (8.3)	11 (15.3)	n.s.
Parotitis n (%)	1 (1.4)	2 (2.8)	n.s.
Herpes infection, n (%)	13 (18.1)	21 (29.2)	n.s.
Tick-borne encephalitis, n (%)	0 (0)	0 (0)	n.s.
Lyme disease, n (%)	0 (0)	0 (0)	n.s.
Toxoplasmosis, n (%)	0 (0)	1 (1.4)	n.s.
Adulthood (18 and older)			
Infectious mononucleosis, n (%)	1 (1.4)	1 (1.4)	n.s.
Acute tonsillitis, n (%)	10 (13.9)	18 (25)	n.s.
Chickenpox, n (%)	8 (11.1)	1 (1.4)	*p*<0.05
Measles, n (%)	0 (0)	0 (0)	n.s.
Rubella, n (%)	0 (0)	0 (0)	n.s.
Pneumonia, n (%)	2 (2.8)	9 (12.5)	n.s.
Parotitis n (%)	0 (0)	0 (0)	n.s.
Herpes infection, n (%)	12 (16.7)	25 (34.7)	*p*<0.05
Tick-borne encephalitis, n (%)	1 (1.4)	0 (0)	n.s.
Lyme disease, n (%)	2 (2.8)	2 (2.8)	n.s.
Hepatitis A, n (%)	0 (0)	0 (0)	n.s.
Hepatitis B, n (%)	3 (4.2)	0 (0)	n.s.
Hepatitis C, n (%)	0 (0)	1 (1.4)	n.s.
COVID-19, n (%)	39 (54.2)	54 (75)	*p*<0.05

Abbreviations in use: n.s. – not significant.

Associations between clinical symptoms and infectious diseases in patients with multiple sclerosis

The descriptive association between past infectious diseases spanning across all life stages (childhood, teenhood, and adulthood) and the presenting syndromes in MS patients was analyzed. A history of acute tonsillitis was reported by 32 (44.4%) patients in the MS group. These patients had a significantly higher frequency of motor (n = 14; $p = 0.025$) and visual (n = 17; $p = 0.047$) impairments. Chickenpox, experienced by 53 (73.6%) MS patients, was significantly associated with a higher rate of sensory deficits (n = 20; $p = 0.027$) and pelvic organ dysfunction (n = 17; $p = 0.034$). Pneumonia, reported by 19 (26.4%) patients, was frequently associated with brainstem dysfunction (n = 16; $p = 0.005$). Furthermore, nearly all patients with a history of pneumonia (n = 18; 94.7%) also reported symptoms related to cerebellar dysfunction ($p = 0.001$). A history of *Herpes* infection, which is present in 17 (23.6%) patients, was significantly linked to a higher frequency of visual impairments (n = 11; $p = 0.019$). COVID-19 infection was reported by 39 patients (54.2%). While cerebellar dysfunction was the most prevalent symptom in this group, the association was not statistically significant ($p = 0.761$). Due to the low number of cases, statistical analysis was not performed for infectious mononucleosis (n = 1; 1.4%), tick-borne encephalitis (n = 1; 1.4%), or Lyme disease (n = 2; 2.8%), as the results would have been unreliable. No statistically significant associations were observed between the remaining infectious diseases and the presenting symptom groups. A detailed breakdown of the distribution of infectious diseases and associated clinical impairments is presented in Table 2.

Table 2. Comparison of the distribution of syndromes in MS patients with infectious diseases

Infectious diseases	Manifested syndromes of MS patients					
	Sensory (n = 22)	**Motor (n = 42)**	**Pelvic organ dysfunction (n = 30)**	**Visual (n = 29)**	**Brainstem (n = 41)**	**Cerebellum dysfunction (n = 45)**
Infectious mononucleosis, n (%)	0 (0)	0 (0)	0 (0)	1 (3,4) (p = 1)	0 (0)	0 (0)
Acute tonsillitis, n (%)	11 (p = 0.530)	14 (p = 0.025)	11 (p = 0.262)	17 (p = 0.047)	16 (p = 0.288)	17 (p = 0.142)
Chickenpox, n (%)	20 (p = 0.027)	31 (p > 0.9)	26 (p = 0.034)	20 (p = 0.460)	30 (p > 0.9)	34 (p = 0.630)
Measles, n (%)	2 (p = 0.302)	4 (p = 0.560)	2 (p = 1)	1 (p = 1)	2 (p = 0.607)	2 (p = 0.555)
Rubella, n (%)	3 (p = 0.550)	5 (p = 1)	5 (p = 0.301)	3 (p = 1)	4 (p = 1)	4 (p = 0.715)
Pneumonia, n (%)	5 (p = 0.640)	11 (p = 0.964)	6 (p = 0.298)	7 (p = 0.728)	16 (p = 0.005)	18 (p = 0.001)
Parotitis n (%)	3 (p = 0.664)	6 (p = 0.066)	4 (p = 0.156)	3 (p = 1)	3 (p = 0.664)	4 (p = 0.719)
Herpes infection, n (%)	7 (p = 0.277)	8 (p = 0.280)	4 (p = 0.083)	11 (p = 0.019)	8 (p = 0.346)	9 (p = 0.352)
Tick-borne encephalitis, n (%)	0	0	0	0	0	0
Lyme disease, n (%)	1 (p = 1)	1 (p = 1)	1 (p = 1)	0	1 (p = 1)	0
Hepatitis A, n (%)	0 (p = 1)	2 (p = 0.513)	0 (p = 1)	0 (p = 1)	1 (p = 1)	1 (p = 1)
Hepatitis B, n (%)	0	0	0	0	0	0
Hepatitis C, n (%)	1 (p = 1)	3 (p = 0.588)	1 (p = 1)	1 (p = 1)	2 (p = 1)	1 (p = 1)
COVID-19, n (%)	14 (p = 0.285)	24 (p = 0.556)	18 (p = 0.403)	17 (p = 0.542)	21 (p = 0.555)	25 (p = 0.761)

Abbreviations in use: MS – multiple sclerosis.

Relapses in patients with multiple sclerosis after an infectious disease

The infectious diseases that occurred in patients after their MS diagnosis included: acute tonsillitis (n = 3; 6%), chickenpox (n = 2; 4%), *Herpes* infection (n = 8; 16%), Lyme disease (n = 1; 2%), Hepatitis B (n = 2; 4%), and COVID-19 (n = 34; 68%). In total, 50 patients reported experiencing at least one of the infections after their diagnosis. Of these 50 patients, 19 (38%) observed a disease relapse following the infection. The majority of the patients who relapsed (n = 14; 73.6%) were those who had contracted COVID-19. Conversely, 31 patients (62%) did not report any worsening of their MS symptoms despite having an infection post-diagnosis. The remaining 22 members of the MS group stated that they had not experienced any infections since their diagnosis. However, no statistically significant association was found between experiencing an infection post-diagnosis and the occurrence of a disease exacerbation ($p > 0.05$).

Associations between disability and infectious diseases in patients with multiple sclerosis

The mean disability of MS patients according to EDSS was 3.45 (SD ± 1.40). When comparing groups that had suffered from the respective infectious disease and those that had not, for groups that had suffered from acute tonsillitis, chickenpox, mumps, pneumonia, *Herpes* infection, COVID-19, a lower mean EDSS score was observed, but a statistically significant difference was calculated in the group with pneumonia ($p = 0.012$) and COVID-19 ($p = 0.023$). MS patients who had had rubella, mumps, or hepatitis B had a higher EDSS average compared to patients who had not had these diseases, but no statistically significant difference was found ($p > 0.05$). Due to the small number of patients who had infectious mononucleosis, toxoplasmosis, hepatitis A, and hepatitis C, no statistical analysis was performed. When comparing whether a higher number of past infections resulted in higher or lower EDSS scores in patients, a slight negative correlation was observed, indicating that a higher number of infectious diseases was associated with a slightly lower EDSS score for the patient, but the result was not statistically significant ($p = 0.207$). Detailed data are presented in Table 3. Considering the duration of the disease, the EDSS score was converted to an MSSS score, with an average of 6.09 (SD ± 1.93). No correlation was observed between the MSSS score and the number of infections ($p > 0.05$).

Table 3. Distribution of disability according to EDSS score and infectious diseases among the members of the multiple sclerosis group

Infectious diseases	MS group (n = 72)		MS patient disability based by their EDSS score		*p* value
	MS patients who had the disease	MS patients who did not have the disease	MS patients who had the disease	MS patients who did not have the disease	
Infectious mononucleosis, n (%)	1 (1.4)	71 (98.6)	5	3.43±1.40	n.s.
Acute tonsillitis, n (%)	32 (44.4)	40 (55.6)	3.09±1.46	3.74±1.31	n.s.
Chickenpox, n (%)	53 (73.4)	19 (26.6)	3.30±1.35	3.87±1.50	n.s.
Measles, n (%)	7 (9.7)	65 (90.3)	3.79±1.60	3.42±1.39	n.s.
Rubella, n (%)	4 (5.6)	68 (94.4)	3.00±1.29	3.48±1.42	n.s.
Pneumonia, n (%)	19 (26.4)	53 (73.6)	2.71±1.21	3.72±1.39	$p<0.05$
Parotitis n (%)	6 (8.3)	66 (91.7)	4.00±1.64	3.40±1.38	n.s.
Herpes infection, n (%)	17 (23.6)	55 (76.4)	3.29±1.32	3.50±1.44	n.s.
Tick-borne encephalitis, n (%)	0 (0)	72 (100)	0	3.45±1.40	n.s.
Lyme disease, n (%)	1 (1.4)	71 (98.6)	4.5±0	3.44±1.41	n.s.
Hepatitis A, n (%)	2 (2.8)	70 (97.2)	5±0.71	3.41±1.40	n.s.
Hepatitis B, n (%)	0 (0)	72 (100)	0	3.45±1.40	n.s.
Hepatitis C, n (%)	3 (4.2)	69 (95.8)	3.50±1.73	3.45±1.40	n.s.
COVID-19, n (%)	39 (54.2)	33 (45.8)	3.10±1.40	3.86±1.31	$p<0.05$

Abbreviations in use: MS – multiple sclerosis; EDSS – Expanded Disability Status Scale; n.s. – not significant.

Discussion

To the best of our knowledge, this is the first study in Lithuania to evaluate the history of infectious diseases in patients with MS and explore statistical associations with their clinical symptoms and disability. The results of this exploratory study provide descriptive epidemiological insights into the potential impact of infections on the clinical course of MS in this specific region.

The most commonly reported infections among our MS patients were chickenpox (73.6%), COVID-19 (54.2%), and acute tonsillitis (44.4%). In international neuroepidemiological studies, the prevalence of chickenpox was noted to be 81.9% in MS patients versus 39.0% in controls [7]. Our study found that while chickenpox was more common in the control group during childhood, its prevalence was significantly higher among MS patients in adulthood ($p < 0.05$). The measles virus has been proposed as a potential contributor to MS pathogenesis; however, its prevalence was low in both our MS group (5.6%) and control group (9.7%), which is a finding that may be attributable to the success of the national MMR vaccination program.

In our cohort, *Herpes* infection was more common in the control group at every life stage, with the difference being statistically significant in adulthood. This contrasts with some findings, such as an Italian population study that reported significantly lower HSV IgG titers in MS patients compared to controls [8]. Comparing the prevalence of other infections with international studies was challenging, as very few recent studies have investigated these specific associations.

A key finding of this study is the descriptive statistical association between specific past infections and distinct neurological symptom patterns: acute tonsillitis with motor and visual deficits, chickenpox with sensory and pelvic dysfunction, pneumonia with brainstem and cerebellar symptoms, and *Herpes* infection with visual deficits. However, given the exploratory nature of the analyses, these specific associations must be interpreted strictly as hypothesis-generating investigation. The large number of uncorrected statistical tests performed fundamentally limits the reliability of these results, and it is highly probable that several of the statistically significant *p*-values represent chance findings (Type I errors). Furthermore, the reliance on subjective retrospective recall – especially for childhood infections – introduces a major risk of misclassification bias between the MS and control cohorts.

Among the 50 patients who experienced an infection after their MS diagnosis, 19 (38%) reported a subsequent relapse. However, we found no statistically significant association between a specific infection and the occurrence of a relapse. This result is consistent with an Italian study which also found no increased relapse risk following clinically manifest infections [9]. It is important to note, however, that other research, particularly concerning COVID-19, has suggested that infections can indeed trigger relapses [10]. The literature suggests that pathogens like EBV may increase the risk for relapsing MS, while HHV-6 and *Chlamydia pneumoniae* may contribute to the development of progressive forms [11,12].

When examining disability by using the *Expanded Disability Status Scale* (EDSS), we observed that patients with a history of certain infections, including pneumonia and COVID-19, had a lower mean EDSS score. However, this finding must be interpreted with extreme caution. Since our analysis did not adjust for critical confounding factors such as the age, exact disease duration, specific MS phenotype, or the use of *Disease-Modifying Therapies* (DMTs), these unadjusted EDSS and MSSS differences may be heavily influenced by these unmeasured variables. This is contrary to some studies that have reported a significant worsening in disability and increased EDSS scores following severe COVID-19 infection [13]. This discrepancy could be explained by several factors not fully controlled for in our study, such as the patients' overall immune status, unrecorded COVID-19 vaccination history, and specific treatments received.

Limitations

Several significant limitations of this study must be explicitly acknowledged. Most critically, the infection data rely heavily on retrospective self-reporting, particularly for childhood infections and in the control group. This subjective approach introduces a major risk of recall bias and misclassification. Furthermore, extensive statistical testing was performed without any adjustment for multiple comparisons, which means that the observed associations are purely exploratory and may include chance findings. Our EDSS and MSSS analyses also lacked control for important confounding factors, such as the age, disease duration, MS phenotype, and the use of disease-modifying therapies (DMT). Additionally, we did not systematically record the vaccination history or healthcare utilization behaviors of the control group, which could serve as unmeasured confounders affecting their exposure to and recall of infections compared to the clinical cohort. This study was also unable to analyze the association between the infectious history and the MS disease course (i.e., relapsing vs. progressive forms) due to the small sample of patients with primary progressive MS (n = 2). A significant limitation was also the inability to analyze the role of Epstein-Barr virus (EBV), as only one case of infectious mononucleosis was reported in each group, and the lack of serological testing prevented the assessment of asymptomatic carriage. Because of these design and data limitations, this study cannot provide definitive answers about the impact of infections on MS development or course but rather serves to generate hypotheses.

Conclusions

This exploratory study provides descriptive epidemiological data highlighting differences in infection histories between MS patients and matched controls in a Lithuanian cohort. The most common self-reported infection in the MS group was chickenpox, particularly in adulthood, whereas the control group most frequently reported COVID-19. Descriptive statistical analyses suggested potential associations between specific infections and clinical manifestations: acute tonsillitis with motor/visual impairments, chickenpox with sensory/pelvic organ dysfunction, pneumonia with brainstem/cerebellar dysfunction, and *Herpes* infection with visual impairments. Patients with a history of pneumonia or COVID-19 had a lower mean EDSS score. However, these findings are hypothesis-generating rather than definitive. The exploratory nature of the observed associations, which rely heavily on retrospective recall and uncorrected statistical tests, require confirmation in larger, prospectively collected, and serology-based studies.

Author contributions

N. V.: Conceptualization, Methodology, Formal Analysis, Investigation, Writing – Original Draft Preparation, Visualization.
R. V.: Writing – Review and Editing.
R. B.: Conceptualization, Methodology, Project Administration, Supervision, Visualization, Writing – Review and Editing.

Conflict of Interest Statement

The authors declare no conflict of interest.

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