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Disease relapses in multiple sclerosis can be influenced by air pollution and climate seasonal conditions

Uticaj zagađenja vazduha i klimatskih uslova na pojavu relapsa multiple skleroze

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Abstract

Background/Aim. Environmental factors may influence the disease activity in patients with relapsing-remitting multiple sclerosis (MS). The aim of this study was to evaluate the influence of air pollution and seasonal climate factors of any on number of relapses in MS patients during a consecutive 5 years of observation. **Methods.** We retrospectively analyzed data of MS patients from the town of Niš, hospitalized at the Clinic of Neurology, Clinical Center Niš, Serbia, from 2005 to 2009. Climate data: mean daily sun shining; mean monthly sun shining, mean whole daily cloudiness, daily cloudiness at 7 a.m, 2 p.m. and 9 p.m. and air pollution expressed by NSR (New Source Review) were obtained from the Meteorology Observatory Niš. **Results.** During a 5-year of observation there were 260 relapses in 101 MS patients. The number of relapses showed a significantly negative correlation with the number of days with NSR < 2 ($\varrho = -0.31$; $p < 0.01$) and a positive correlation with the mean whole daily cloudiness ($p < 0.05$), mean daily cloudiness at 7 a.m. ($p < 0.05$) and 2 p.m. ($p < 0.01$). We found a significantlly positive correlation ($p < 0.05$) between the reduced number of relapses during the period of high vitamin D season, i.e. July–October. There was a statistically significant increase ($p < 0.01$) of the number of relapses during spring ($\bar{x} = 6.53$; SD = 3.98) compared to the other three seasons. The joint presence of lower number of days with NSR < 2 during low vitamin D season (January–April) correlated with a statistically significant increase of the number of relapses in MS patients ($F = 5.06$, $p < 0.01$). **Conclusion.** The obtained results confirmed the influence of air pollution and climate seasonal conditions on disease relapses in MS patients based on a long-term observation. Lower numbers of days with low air pollution during the periods with low vitamin D (January–April), especially with increased cloudiness at 2 p.m, induce a higher risk of MS relapses in southern continental parts of Europe.

Key words:
multiple sclerosis; recurrence; air pollution; climate; sunlight; vitamin d.

Apstrakt

Uvod/Cilj. Nekoliko istraživanja ukazalo je na mogućnost uticaja klimatskih faktora na aktivnost bolesti u relapsno-remitentnoj multiploj sklerozi (MS). Cilj istraživanja bio je da se ispita uticaj zagađenja vazduha i sezonskih klimatskih faktora na pojavu relapsa bolesti u dužem vremenskom periodu. **Metode.** Retrospektivno i detaljno statistički analizirali smo podatke o broju relapsa MS bolesnika iz Niša i okoline, hospitalizovanih u Klinici za neurologiju Kliničkog centra Niš, od 2005. do 2009. godine. Praćeni su klimatski faktori: srednja mesečna osunčanost, srednja dnevna oblačnost, dnevna oblačnost u 7, 14 i 19 časova i stepen zagađenja vazduha meren po metodu *New Source Review* (NSR), a na osnovu podataka Meteorološke stanice Niš. **Rezultati.** Tokom pet godina praćenja 101 bolesnika registrovano je 260 relapsa MS čija pojava je imala statistički značajnu negativnu korelaciju sa brojem dana sa niskim nivoom zagađenja vazduha, NSR < 2 ($\varrho = -0{,}31$ $p < 0{,}01$) i pozitivnu korelaciju sa povećanim brojem dana sa povećanom ukupnom dnevnom oblačnošću ($p < 0{,}05$), kao i oblačnošću u 7 ($p < 0{,}05$) i 14 časova ($p < 0{,}01$). Prosečan broj dana sa NSR > 8 bio je statistički značajno veći od broja dana sa NSR < 2 tokom 2005, 2006 i 2009. ($p < 0{,}05$). U periodu visokog nivoa viatamina D (jul–oktobar) utvrđena je statistički značajna korelacija sa sniženjem učestalosti relapsa ($p < 0.05$). Broj relapse u proleće ($\bar{x} = 6{,}53$; SD = 3,98) bio je statistički značajno veći ($p < 0{,}01$) u odnosu na leto ($\bar{x} = 3{,}27$; SD = 2,49), jesen ($\bar{x} = 2{,}93$; SD = 1,62) i zimu ($\bar{x} = 4{,}60$; SD = 2,64). U periodima karakterističnim za snižene nivoe vitamina D (januar–april), uz istovremeno prisustvo NSR < 2 primećen je statistički značajan porast broja relapsa MS ($F = 5.06$, $p < 0{,}01$). **Zaključak.** Tokom dužeg vremenskog perioda klimatski faktori utiču na aktivnost MS. Veći broj dana sa povećanom zagađenošću vazduha u sezoni niskog nivoa vitamina D (januar–april), posebno u slučaju povećane oblačnosti u 14 časova, značajno povećavaju rizik od pojave relapsa MS u jugoistočnim kontinentalnim delovima Evrope.

Ključne reči:
multipla skleroza; recidiv; vazduh, zagađenje; klima; sunčeva svetlost; vitamin d.

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Introduction

Multiple sclerosis (MS) is a chronic immune-mediated inflammatory-demyelinating disease of the central nervous system (CNS). It is postulated that, beside genetic susceptibility, environmental factors may play a crucial role in the disease origin [1]. Epidemiological studies have found that risk to develop MS and the disease prevalence is enhanced with the latitude and by changing the residence from the equator to northern areas [2, 3]. The inverse correlation between risk to develop MS and previous sunshine exposure is found in several studies in the USA [4], Norway [5], Canada [6] and Australia [7].

Environmental factors also can have impact on the disease activity influencing relapse triggering[1] and the disease seasonal variability [8–11]. A higher frequency of relapses is often associated with lower vitamin D serum levels, lower sunshine ultraviolet (UV) radiation exposition and high frequency of infections [11]. UV radiation is the prime determinant of the circulated serum vitamin D level and it highly depends on the regional weather conditions[12]. Soilu-Hanninen et al.[13] have found that lower serum vitamin D level during relapse could be in relation to remission in MS patients while Simpson et al.[14] have shown that higher vitamin D serum levels are associated with lower relapse risk in MS patients.

The effects of air pollution on the pulmonary and cardiovascular systems have been well-established in a series of major epidemiological and observational studies, but newer data indicated a possible association with diseases of the CNS, including stroke, Alzheimer's disease, Parkinson's disease and neurodevelopmental disorders. Emerging evidence indicated that air pollution could provoke neuroinflammation, oxidative stress, microglial activation, cerebrovascular dysfunction and alterations in the blood-brain barrier [15]. Air pollution and poor air quality are related to the risk of multiple sclerosis in women, as well as exacerbation of symptoms as shown in a study correlating outdoor air particulate matter (PM) and the occurrence of MS in women in the Atlanta area. PM is a particulate matter from smoke, dirt and dust from factories, farming and roads, mold, spores, and pollen and can affect the immune system making those exposed more susceptible to infections. PM has an influence on systemic immune response and inflammation. Ambient air pollutants are known to induce systemic immune responses and to enhance existing peripheral inflammation. Ambient air quality and monthly MS relapse occurrence in south-western Finland were compared showing that the risk of relapse was by over fourfold increased when the concentration of PM was at the highest quartile [16, 17].

The majority of other investigated climate factors (maximal and minimal air temperature, air humidity, level of precipitations or atmospheric pressure) did not show a significant correlation with the relapse frequency in MS patients [18–20].

There are only few studies investigating this topic and increasing queries from MS patients. Since geographic determinants and country industrial and economic development can influence the obtained results, it is necessary to investigate insolation, air pollution and other climate factors on MS in different parts of the world to gather conclusive information. This is why the aim of this study was to investigate if there is a correlation between the frequency of relapses in MS patients during the year and climate factors which may influence sunshine accessibility.

Methods

This cross-sectional retrospective study included patients with the established diagnosis of MS with relapsing-remitting disease course according to the McDonald criteria [21] independently on disease duration. We analyzed the disease activity expressed through the relapse frequency in patients hospitalized at the Clinic of Neurology, Clinical Center Niš, Serbia (referral institution covering the area with ~ 2 million inhabitants) from 2005 to 2009. Serbia is a typical non-EU developing country at the southern Europe with typical four seasonal climates. Only patients settled in the urban parts and rural suburbs, of the Niš municipality localized in south-east Serbia (43.3000°N, 21.9000°E) were enrolled into the study.

The exclusion criteria were treatment with immunomodulatory drugs during the observational period and clear evidences of proceeding infection prior to disease relapse. MS relapse was defined as the onset of new objective neurological symptoms/signs or worsening of existing neurological disability, not accompanied by metabolic changes, fever or other signs of infection, and lasting for a period of at least 48 h accompanied by objective change of at least 0.5 in the EDSS [22] score. The diagnosis of MS relapses was established by the neurologist – MS specialist. We analyzed the annual distribution of relapses recorded during 12 months of the year. The study design was approved by the local Ethic Committee and performed in accordance with the Declaration of Helsinki.

Sunshine accessibility was evaluated by the records of meteorology data from the Meteorology Observatory Niš. Over the 5 years (2005–2009) each month we collected monthly data about: mean sun shining expressed by the number of daily sunny hours; monthly sun shining (total hours number); mean whole daily cloudiness; daily cloudiness at 7 am, 2 pm and 9 pm expressed as one tenth (1/10) of the cloudiness of the visible sky and the air pollution expressed by direct air pollutions and their precursors measured as recommended by Environmental Protection Agency (EPA) and its New Source Review (NSR) permits [23]. Air pollution was expressed by the number of days with NSR less than two (low level of air pollution) and the number of days with NSR more than eight (high level of air pollution).

Several epidemiologic studies have shown that there are seasonal, month by month, variations in vitamin D levels not corresponding with classic climate periods that could be divided in three seasons: low (January–April), high (July–October) and medium (May, June, November, December). We used this definition to additionally stratify our data in addition to classic seasonal periods [24–26].

Statistical analysis was performed using Spearman`s coefficient of linear correlation to find a potential correlative connection between the number of monthly relapses and examined parameters. We have used ANOVA test (one way and two way) to test the influence of environmental parameters on the number of relapses during the seasons and performed consequent *post hoc* analysis of the multiple comparisons by Tamhane test. To evaluate monthly variations in relapse number we performed Kolmogorov-Smirnov test to check normality of sample parameters within a 5-year observational period.

Results

Out of 230 MS patients hospitalized at our Clinic who had 497 disease relapses, the inclusion criteria were met in 101 patients, settled in the town of Niš and its suburbs, with 260 relapses recorded during a 5-year observational period. There were 22 males and 79 females with the average age 39.3 years (18–60 years) with no statistically significant differences in age. There were 74 patients settled in the urban parts of Niš and 27 patients settled in rural suburbs. We did not found any statistically significant differences in monthly number of relapses between sexes, nor between the patients settled in rural and urban environment.

The average number of relapses by month and year during the investigated seasonal periods, is shown in Figure 1. The cumulative number of relapses (during 5 years of observation) ranked according to seasonal periods with high, medium and low levels of vitamin D (according to Bell et al. [24]) was significantly higher in the period with low vitamin D level compared to other two seasonal periods ($p < 0.01$) as shown in Figure 1. We found a significant positive correlation ($p < 0.05$) between reduced number of relapses during the period of high vitamin D season [24] i.e. July–October. Statistical analysis using χ^2 test to calculate the difference between the expected and observed number of relapses during seasonal periods with high, medium and low vitamin D levels, showed a significant decrease in the number of relapses during the season defined as high vitamin D season (Table 1). Correlation analysis used to compare the number of relapses in different classic climate seasons showed the influence of seasonal variations on the relapse number during a 5-year observational period with a statistically significant increase ($p < 0.01$) relapses of number during spring ($\bar{x}$ = 6.53; SD = 3.98) compared to the other three seasons: summer ($\bar{x}$ = 3.27; SD = 2.49), autumn ($\bar{x}$ = 2.93; SD = 1.62) and winter ($\bar{x}$ = 4.60; SD = 2.64).

Air pollution data (Figure 2) analysis showed the that average number of days *per* month with NSR > 8, during the

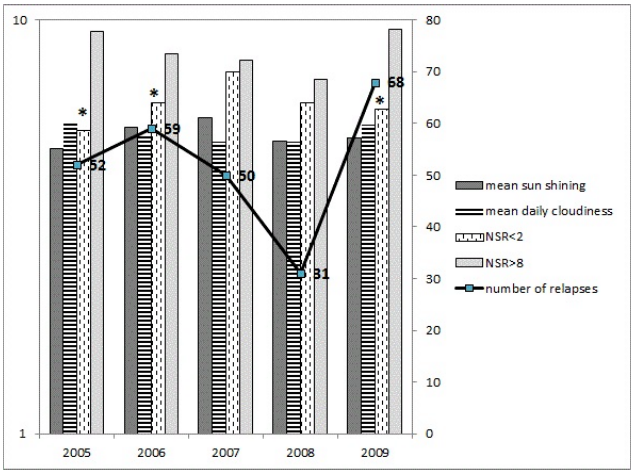

Fig. 2 – Correlation of the average number of relapses with air pollution and climate factors during the observational period (5 years)

Left Y axis – absolute number of values for parameters investigated: the mean sun shining expressed by the number of daily sunny hours, mean whole daily cloudiness expressed as one tenth (1/10) of cloudiness of the visible sky, air pollution expressed by direct air pollutions and their precursors measured as recommended by the Environmental Protection Agency (EPA) and its New Source Review (NSR) permits; Right Y-axis – average number of relapses *per* year; * - statistically significant correlation ($p < 0.01$).

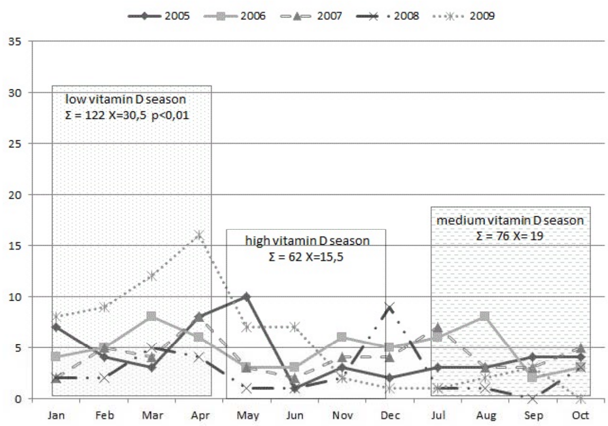

Fig. 1 – Relapse rate by months and years according to the seasonal periods

Y-axis – absolute number of relapses; X-axis – months during year; ∑ – sum of relapses; x – mean number of relapses.

Table 1

Number of relapses during the periods according to vitamin D level

Annual period according to vitamin D levels	Relapse number (sum 2005–2009)		
	observed	expected	other
Low vitamin D	122	86.7	35.3
Medium vitamin D	76	86.7	-10.7
High vitamin D	62	86.7	-24.7
Σ 2005–2009	260		

χ^2 = 22.77 ; df 2 ; $p < 0.001$.

observational period, was higher than the number of days with NSR < 2 with a statistically significant difference in 2005, 2006 and 2009 ($p < 0.05$). The number of relapses showed a significantly negative correlation with the number of days with NSR < 2 ($\rho = -0.31$; $p < 0.01$), indicating the increased number of relapses during the periods with small number of days with low air pollution. ANOVA test and the consequent *post hoc* analysis of multiple comparisons using the Tamhen test showed a joint presence of two factors, i.e. low number of days with NSR < 2 during the low vitamin D season (January–April) inducing statistically significant increase in the number of relapses in MS patients (F = 5.06, $p < 0{,}01$).

The mean daily sun shining expressed by the number of daily sunny hours and the mean whole daily cloudiness expressed through one tenth part of the visible sky was stabile during the observation (Figure 2). Both sunshine parameters measured (the number of sunshine hours per day and the sum of sunshine hours/day/months) did not influenced the number of relapses recorded.

The results of Spearman's linear correlation analysis between the number of monthly relapses and the examined climate parameters are presented in Table 2. Monthly relapse number showed a statistically significant positive correlation with the mean whole daily cloudiness ($p < 0.05$), the mean daily cloudiness at 7 am ($p < 0.05$) and mean daily cloudiness at 2 pm ($p < 0.01$).

Table 2

Correlations of the monthly number of relapses with the investigated climate factors

Climate factors	ρ	*p*
Mean sun shining (number of hours/day)	-0.18	0.1809
Monthly sun shining (sum of hours/day/months)	-0.18	0.1796
Daily cloudiness (as 1/10 of the visible sky)	0.29	0.0240*
Mean daily cloudness (at 7 am as 1/10 of the visible sky)	0.28	0.0325*
Mean daily cloudness (at 2 pm as 1/10 of the visible sky)	0.34	0.0074#
Mean daily cloudness (at 9 pm as 1/10 of the visible sky)	0.24	0.0655
Number of days/year with NSR < 2	-0.32	0.0115#
Number of days/year with NSR > 8	0.21	0.1081

NSR – New Source Review; ρ - correlation coefficient; *- $p < 0.05$; # - $p < 0.01$.

Discussion

There are several ambient environmental factors most frequently considered to influence different relapse rates in MS patients such as sun shining, rainfall, ozone or air pollution [17] and cycle fluctuations of infections[11]. Tremlett et al. [11] investigated a connection between MS and ambient factors and found a significant connection between the relapse rate and UV radiation induced erythemal level. Instead of cloudiness they analyzed the level of rainfall and did not find any statistically significant connection. The same study analyzed the influence of air pollution (expressed by aerodynamic particulate of a defined diameter – PM10) on the relapse rate and could not finding clear statistical connection.

The results of our study did not confirm any connection between the disease activity and direct sunshine accessibility measured by the number of sunshine hours *per* day and the sum of sunshine hours/day/months but showed the indirect connection with sunshine accessibility through the degree of cloudiness. The first connection between sun shining and MS was pointed out by Sir Donald Acheson et al. [4] in 1960 while later findings pointed out that sunshine influence on MS is indirect and correlate with vitamin D levels and its immunomodulatory effects. Immunomodulatory effects of vitamin D in MS were confirmed by the results of experimental and human investigations [27–30]. The influence of vitamin D on MS even could be independent from the level of sunshining which has been confirmed by epidemiological studies in Eskim populations who should have high risk for MS according to the low level of sunshining, but have been found to have low MS morbidity [31]. Nevertheless some recent studies have shown evidence that sunshine supress the clinical signs of animal model of MS – experimental autoimmune encephalomyelitis independent on vitamin D level [32].

According to the fact that sunshine UV accessibility is not determined only by insolation intensity and duration but also by the structures on the sunshine way to the earth, this result may be explained by a higher absorption and/or scattering of sunshine UV rays by clouds and air pollutants [33–35]. Our finding of a statistically significant correlation between the number of relapses and the mean whole daily cloudiness, mean daily cloudiness at 7 a.m. and 2 p.m. and the degree of air pollution (lower number of monthly days with NSR < 2) is in accordance with this.

There are numerous studies with controversial results about seasonal variation in the MS disease activity. Some of them have found the presence of seasonal variability in the number of relapses in MS patients [8–11, 36, 37] while other did not find a clear seasonal character of the disease [18, 38, 39]. Embry et al.[40] study supported the finding of seasonal fluctuations by a correalation with the number of gadolinium contrast enhancing lesions on MRI which tend to get lower in the period when serum 25(OH)D is higher which is in accordance with the findings of seasonal variations in vitamin D levels (beeing lower during winter and higher during summer) [41].

Our results clearly demonstrated statistically significant increase in the number of relapses during spring compared to the other three seasons: summer, autumn and winter during 5 years of observation. This confirmed the findings of Tremllet et al. [11] who have found a lower frequency of relapse appearing in summer than in winter in the context of the evident positive correlation between serum levels of vitamin D and relapse frequency, but also in the context of a higher frequency of upper respiratory tract infections. On the other hand, our results support observations that the classic climate four-season approach do not necessarily correlate with the influence of vitamin D since there is almost a 2-month difference between 25(OH)D decrease and the appearance of MS worsening or increased number of relapses and *vice versa* [40]. This was the main reason why we decided to implement two types of season division approaches: classic climate seasons and seasons according to the average levels of vitamin D [24–26]. Both approaches showed a significant seasonal influence on MS relapse rate but only seasonal variations according to the average levels of vitamin D showed a significant joint impact with cloudiness and air pollution on disease relapse rates during 5 years of observation. Unfortunately, one of the main biases of our study was unavailability of patient's blood samples, due to retrospective nature of the study, to tests real levels of 25(OH) D in our patient cohort.

Conclusion

The impact of air pollution on MS relapse rate, found in our study is in accordance with a recent observation that air pollution could influence neuroinflammation, blood brain barrier functions and neurodegenerative processes in the CNS. The most important finding of our investigation is that a lower number of days with low air pollution during the periods with low vitamin D (January–April), especially with increased cloudiness at 2 p.m, increase risk of MS relapses in the southern continental parts of Europe. Because of this and with respect to conflicting data about seasonal variations (with unclear definition of vitamin D seasonal impact) and the influence of sun shining, climate factors and air pollution, in conclusion we would suggest that further studies investigating any of these factors role in MS, should always take into account the joint effect of several environmental factors through a longer time period.

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