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RELAPSES IN MULTIPLE SCLEROSIS

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Abstract. Relapses In multiple sclerosis. Nikolenko O.O., Shulga O.D., Kozliuk V.V., Zheshko O.M., Yurko O.A., Dubinets M.I. *Exact causes of contradictions in the understanding of relapsing course as characteristic phenomenon of multiple sclerosis (MS) and primarily relapsing-remitting type are still considered to be "sub rosa". We tried to determine connection and correlation between seasonal dynamic factors, chronometric parameters of disease progression (age, disease duration) and frequency of relapses and the role of gender differences as well. A four-year prospective study included complete registration of all cases of MS exacerbations in resident patients with a relapsing-remmiting course of the disease according to McDonald criteria in Volyn region of Ukraine in 2010. Each patient had neurological score based on EDSS scale to ensure compliance with inclusion criteria. 128 patients (44 males and 84 females) with a remitting-recurring course of the disease were involved in this study. Statistical analysis was performed using SPSS 18, MedCalc and Microsoft Excel software using standard descriptive statistics, correlation and regression analysis. In total, 197 cases of MS relapses were registered. Episodes of relapses prevailed in winter-spring period. Multiple regression model including suggested climate factors showed multiple correlation coefficient – 0.55 (p<0.01). The prevalence of MS was higher in females, while general incidence of recurrences was similar to males. However, relapse rate in different age groups differs: the rate of recurrence increases in women aged after 50 years (mean annualized relapse rate (ARR)=0.66), while it slowly decreases in men with aging. The duration of the disease did not have significant effect on the course of MS in women, whereas weak negative relationship (0.24, p<0.001) between the duration of the disease and the frequency of MS in men was showed. Correspondingly, the average negative correlation (-0.37, p<0.001) was detected between the age of disease onset and the incidence of MS recurrence in males, while this connection was not observed in females. We established that the recurrence of MS is a result of multifactorial influence of external and internal factors. Individual seasonal climate variability did not have sufficient force of influence. Therefore, combined effect of corresponding climate changes played a significant role. Furthermore, it is quite probable that interactions of MS with external factors influencing the human body can be mutually integrated.*

Реферат. Загострення при розсіяному склерозі. Ніколенко О.О., Шульга О.Д., Козлюк В.В., Жешко О.М., Юрко О.А., Дубінець М.І. *Точні причини суперечностей у розумінні загострень як характерного явища розсіяного склерозу (РС) і головним чином рецидивуючого-ремітуючого типу досі вважаються «sub rosa». Ми намагалися визначити зв'язок та кореляцію між сезонними динамічними факторами, хронометричними параметрами прогресування захворювання (віком, тривалістю захворювання) та частотою рецидивів, а також впливом гендерних відмінностей. Чотирирічне проспективне дослідження передбачало повну реєстрацію всіх випадків загострення РС у пацієнтів-резидентів з ремітуючим-рецидивуючим перебігом захворювання за критеріями McDonald 2010 у Волинській області України. Кожен пацієнт був оцінений за шкалою EDSS для забезпечення відповідності критеріям включення. У цьому дослідженні для подальшого аналізу за допомогою статистичних даних було залучено 128 пацієнтів (44 чоловіки та 84 жінки) з ремі-туючим-рецидивуючим перебігом захворювання. Статистичний аналіз проводили за допомогою програм SPSS 18, MedCalc та Microsoft Excel, використовуючи стандартну описову статистику, кореляційний та*

регресійний аналіз. Загалом зареєстровано 197 випадків рецидивів РС. Епізоди рецидивів переважали в зимово-весняний період. Модель множинної регресії, включаючи запропоновані сезонні кліматичні фактори, показала множинний коефіцієнт кореляції – 0,55 (p<0,01). Поширеність РС була більшою в жінок, разом з тим загальна частота рецидивів була схожа на частоту серед чоловіків. Було встановлено, що частота рецидивів у різних вікових групах відрізняється: частота рецидивів збільшується в жінок у віці після 50 років (середня річна частота рецидивів (ARR)=0,66), тоді як вона повільно знижується в чоловіків з віком. Тривалість захворювання не мала суттєвого впливу на перебіг РС у жінок, тоді як слабкий негативний зв'язок (0,24, p<0,001) був виявлений між тривалістю захворювання та частотою РС у чоловіків. Було встановлено середню негативну кореляцію (-0,37, p<0,001) між віком початку захворювання та частотою рецидиву РС у чоловіків, у той час як у жінок такого зв'язку не спостерігалось. Ми встановили, що загострення при РС спричинені багатофакторним впливом зовнішніх та внутрішніх факторів. Індивідуальна сезонна мінливість клімату не мала достатньої сили впливу. Комбінований ефект відповідних змін клімату відіграв значну роль. Крім того, цілком ймовірно, що взаємодії РС із зовнішніми факторами, що впливають на організм людини, можуть взаємно інтегруватися.

Multiple sclerosis (MS) is a disease with chronic course and uncertain underlying cause which affects young adults. In the world, there are from 2 to 3 million patients suffering from MS [3, 4]. Relapse (exacerbation) is a phenomenon inherent to the clinical course of MS. Relapses of MS result in a number of social and economic consequences. Short-term negative effects of exacerbations include the impossibility of performing routine work and family work due to the hospitalization, often the loss of work through limitation of mobility or ability to drive. Exacerbations in MS also contribute to a number of psychological problems, such as: reduced mood of patients due to uncertainty of disease course and prognosis, anxiety and depression. The long-term effects of exacerbations of MS include shortening of the term to functional dependence and shortening the interval to the progression of MS [3].

Frequency of relapses can be connected with seasonal factors. According to conducted studies [1, 6, 8, 11, 12] there are seasonal deviations of relapses.

Chronometric factors associated with increased probability of relapse include early onset and short duration of the disease. There are peculiarities in the dynamics of relapse due to gender: it occurs more frequently in men than in women. There are more significant indicators of early disability, whereas higher frequency of exacerbations in time section is observed in women [7].

The peculiarities of relapses were not studied in population of Ukrainian patients with MS before. The aim of the study was to find out the influence of age, gender, time factors and climate factors on the occurrence of MS relapses in a relapsing-remitting course during 4 years of prospective observation.

MATERIALS AND METHODS OF RESEARCH

Our study included complete and accurate registration of all cases of MS relapses in patients with a relapsing-remitting course of the disease according to McDonald 2010 criteria at Volyn region of Ukraine. Each case of MS relapse was con-firmed by EDSS scale to ensure compliance with inclusive criteria. 128 patients (44 males and 84 females) aged 18-70 years were involved in this study.

Prospective study was conducted from January 2014 to January 2018 in the Multiple Sclerosis Center in Volyn Regional Clinical Hospital (covering the area of 1 million population). Relapses (exacerbations) of MS were regarded as the development of new symptoms or worsening of existing ones, lasted more than 24 hours, without elevation of body temperature or evidence of infection. Relapses, that all patients had undergone were treated as separate cases of exacerbation only if there was about one month interval between them. Pseudo-attacks associated with changes in body temperature due to an infectious process and lasting less than 24 hours, were excluded.

We analyzed seasonal dynamics of MS in terms of monthly changes against the climate background, as Volyn region is an endemic zone of multiple sclerosis in Ukraine. Thus, we used aggregated weather data from the manual "Reference data about the climate of Ukraine" [2]. Due to the absence of available similar reports from 2015 to 2017, therefore, data were computed for the period of 2014 to conduct complete assessment of the correlation between individual climate factors and MS relapses.

However, records of the average temperature and precipitation data for 2014-2017, taken from the reports of the Central Geophysical Observatory named after Boris Sreznevsky [5], located in the capital of Ukraine – Kyiv, showed the absence of gross fluctuations in the schedule of climate curves compared to the period of 2014. Therefore, we suggested to cover patterns found in the analysis during the period of 2014 for all time observations (2014-2018). We also offered to consider results of our study of seasonal recurrence of multiple sclerosis as approximate but at the same time as sufficiently indicative due to the afore-mentioned annual climate dynamics during 2014-2018 (Four-Year Plan).

Patients were divided into two main groups by gender for detailed analysis. Following age categories were introduced: for men – 20-39years and ≥40 years; for women – 20-39 years and ≥40 years. In addition, there was a group of women aged over 50 years, as menopause period usually begins at this age and significantly affects the level of hormones in the blood. A group of men aged over 50 years were as restriction to the same division. We considered patient's average age at the time of the survey, the average age of the disease onset, as well as the duration of the disease in order to evaluate chronometric rate of the disease. To give an overall assessment of the frequency of exacerbations by sex, we also took into account average annualized relapse rate (ARR), indicator of relapse, regarded as the ratio of total number of patients' exacerbations, males or females, respectively, to number of patients of the same sex in a 4-year period.

Statistical analysis was performed using SPSS 18, Statistica, MedCalc and Microsoft Excel software, standard descriptive statistics, correlation and regression analysis. Potential correlation between the number of monthly relapses and investigated parameters was conducted according to Spearman's correlation coefficient. As already mentioned, climate data were only available for the period of 2014 therefore, methods of logistic regression were not used. But analysis of monthly recurrence using multiple regressions to specifically assess the impact of clinical to changes on the probability of relapse, allowed create climate model of MS relapsing with significant factors – tavg, tmin, wind speed, albedo and partial pressure of water vapor ($p<0.01$).

RESULTS AND DISCUSSION

In total, 197 exacerbations were registered from January 2014 to January 2018 in patients with remitting-recurring type of MS (N=128). The group aged from 20 to 40 years included 71 patients: 22 men and 49 women respectively; 57 patients aged over 40 years old: 22 men and 35 women; 8 separately categorized women aged over 50 years. The analysis of relapse in males aged over 50 was performed despite small group selection. Thus, 84 women (65,62%) prevailed among examined patients with MS in comparison to 44 men (34,37%), respectively.

Average patient's age in men and women was insignificantly different during the study: males – 39 years (95% CI 36.5 to 41.5) and females – 38 years (95% CI 36.2 to 39.8). Average age of the onset of the disease was 27 years for men (95% CI 23.2 to 28.8) and 30 years for women (95% CI 27.2 to 30.8). Duration of the disease was 13 years in men (95% CI 9.54 to 14.5) and 8 years in women (95% CI 7.0 to 8.99).

General characteristics data of patients with MS and calculated chronometric parameters of disease are summarized in Table 1.

T a b l e   1

Patients' characteristics

Indicator	Value
In total:	
Women	**97**
Men	**31**
Mean current age (years):	
Women	**38 (95% CI 36.2 to 39.8)[1]**
Men	**39 (95% CI 36.5 to 41.5)[1]**
Mean age at onset (years):	
Women	**30 (95% CI 27.2 to 30.8)[1]**
Men	**27 (95% CI 23.2 to 28.8)[1]**
Mean disease duration (years):	
Women	**8 (95% CI 7.0 to 8.99)[1]**
Men	**13 (95% CI 9.54 to 14.5)[1]**

Note. [1] 95-percent of confidence interval.

Basic analysis of monthly frequency of MS exacerbations showed prevalence of recurrence in winter (27%) and in spring (32%) during the period from 2014 to 2018. The rarest cases of exacerbations were recorded in summer. Average monthly total exacerbation rate (n=128) was >5 cases per year during February-April and ≤5 cases in other months were noted among all MS patients. Monthly exacerbations in patients varied in women and men (Fig. 1, Fig. 2).
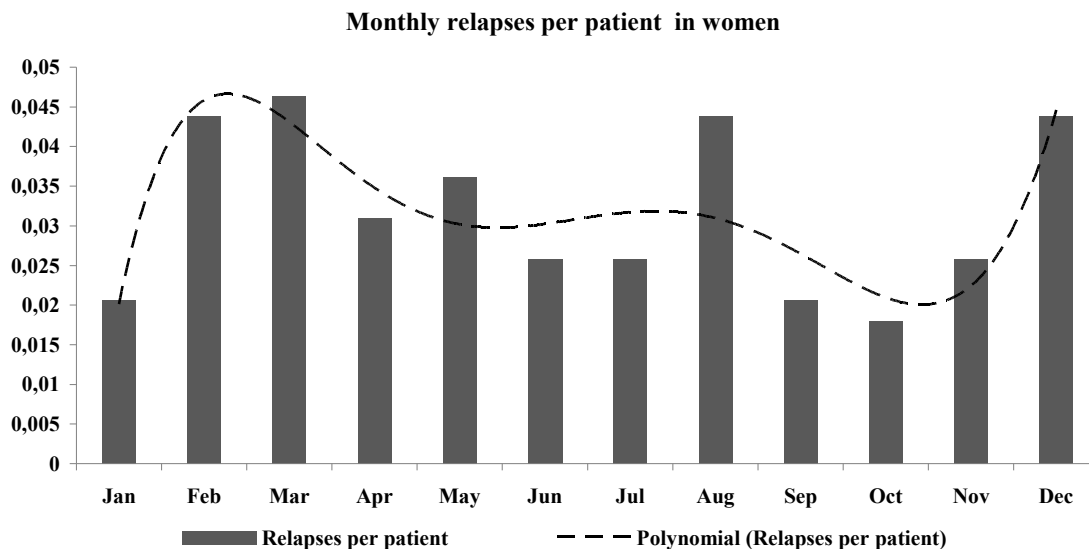
Monthly relapses per patient in women

Fig. 1. The mean number of exacerbations in women per month during the period from 2014 to 2018 and polynomial trend line
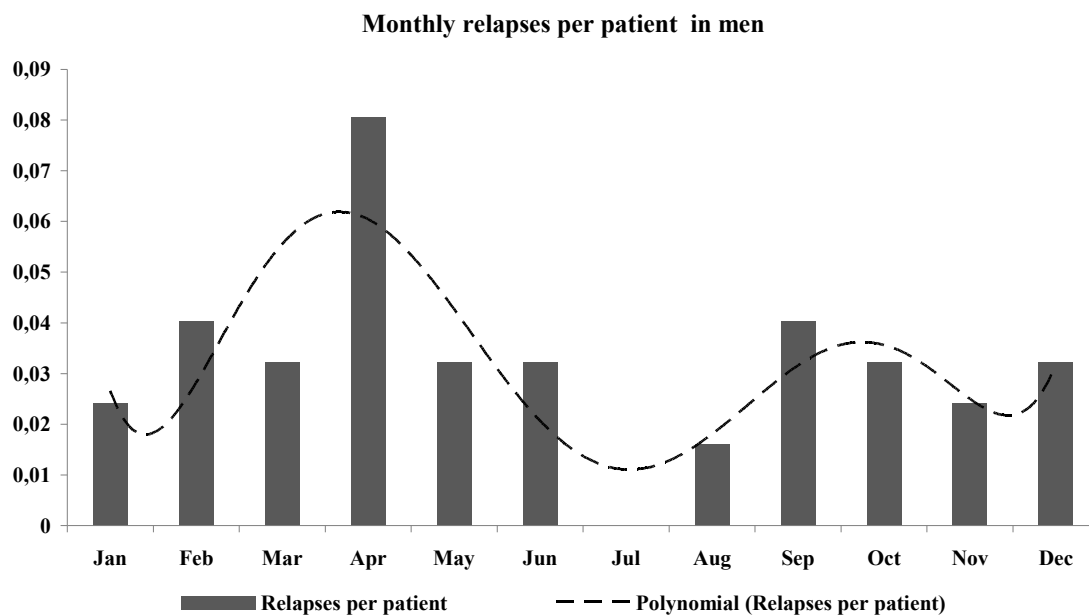
Monthly relapses per patient in men

Fig. 2. The mean number of exacerbations in men per month during the period from 2014 to 2018 and polynomial trend line

Monthly meteorological data in Volyn region are shown in Table 2.

Spearman's correlation coefficient between environmental factors and MS relapses showed weak negative correlation (0...-0.299) for average and average maximum temperatures, saturation deficits, direct, scattered and total solar radiation, radiation balance, sunlight duration, fog, thunderstorms; average negative connection (-0.3...-0.699) for partial pressure of water vapor (-0.36, p-value =0.0113), average and minimal temperature (-0.31, p-value =0.0320;

-0.32, p-value =0.0257); weak positive correlation (0...-0.299) for cloudiness and relative humidity; average positive correlation (0.3...-0.699) for wind speed (0.40, p-value = 0.0054) and albedo (0.32, p-value = 0.0266) (Tab. 3, Fig. 3).

Multiple regression model (including climate factors as average and minimal temperature, wind speed, albedo and partial pressure of water vapor) showed multiple correlation coefficient – 0.55. Significance level was 0.008.

Table 2

Monthly meteorological data in Volyn region of Ukraine (year 2014)

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Tavg	-4,6	-3,7	0,4	7,2	13,9	17	18,6	17,4	13,2	7,4	2,4	-2,2
Tmax	-1,8	-0,5	4,5	12,5	19,8	22,9	24,5	23,3	19,1	12	5,1	0,4
Tmin	-7,6	-6,7	-2,7	2,8	8,6	11,3	13,3	12,4	8,4	3,6	-0,1	-4,6
PPoWV	4	4,2	4,9	7,6	10,6	13,7	15,2	15	11,7	8,4	6,8	5
RH	85	85	80	72	68	70	72	76	78	82	88	88
DoS	0,7	0,7	1,4	3,6	5,9	7	7,3	5,9	4	2,1	1	0,7
S'	25	49	107	188	283	317	295	264	170	77	22	9
D	63	101	179	212	288	298	303	252	179	112	53	46
Q	88	150	286	401	570	615	598	516	347	189	74	55
B	-34	-16	35	178	287	332	308	228	148	51	-14	-18
Ak	73	71	58	24	22	22	21	21	22	23	37	64
T	51	69	122	181	255	222	287	251	194	105	43	31
WS	4,6	4,6	4,4	4	3,5	3,3	3	2,8	3,1	3,5	4,1	4,4
GC	7,6	7,7	6,9	6,6	6,2	6	5,9	5,5	5,7	6,5	8,2	7,9
LC	5,9	6	4,8	4,2	3,8	3,9	3,6	3,3	3,5	4,7	6,7	6,4
Mists	5	5	4	2	1	2	2	2	4	6	5	7
SM	0	0	0,2	1	5	6	7	5	2	0,4	0	0
SMx	0	0	2	5	13	12	16	9	6	3	0	0
Hail	0	0	0,06	0,2	0,5	0,4	0,3	0,05	0,2	0,04	0	0
Sun dur.	259	279	365	413	481	497	501	454	382	335	268	245

Note. Tavg - average air temperature (degrees Celsius); tmax - average maximum temperature (degrees Celsius); tmin - average minimum temperature (degrees Celsius); PPoWV – partial pressure of water vapor; RH – relative humidity; DoS - deficiency of saturation; S' - direct solar radiation entering the horizontal surface (MJ / m²); D - scattered radiation (MJ / m²); Q - total radiation (MJ / m²); B - radiation balance (MJ / m²); Ak - albedo (%); T - duration of sunshine (year); WS – wind speed; GC – general cloudiness; LC – lower cloudiness; SM – storm medium; SMx – storm maximum; Sun dur. – sun duration.

Correlations between suggested climate factors and the number of relapses in MS per month

Climate factors	P¹	p-value
Tavg	-0,31	0,0320
tmax	-0,29	0,0450
tmin	-0,32	0,0257
Partial pressure of water vapor	-0,36	0,0113
Relative humidity	0,02	0,9090
Deficiency of saturation	-0,24	0,0989
S'	-0,1	0,4934
D	-0,03	0,8276
Q	-0,07	0,6418
B	-0,16	0,2922
Ak	0,32	0,0266
T	-0,13	0,3932
Wind speed	0,40	0,0054
General cloudiness	0,19	0,2039
Lower cloudiness	0,12	0,4252
Mists	-0,04	0,7890
Storm medium	-0,27	0,0636
Storm max	-0,26	0,0688
Hail	-0,14	0,3463
Sun duration	-0,10	0,4877

Note. [1] p - Spearmen's correlation coefficient.

Results of our study evidently presented statistically significant increase in number of relapses in winter-spring period compared to summer and autumn. These results were similar to previously performed studies and can be partially explained by common triggers of relapses such as lower serum level of vitamin D during winter time and higher prevalence of upper respiratory tract infections in winter and spring [9, 13].

Understanding the role of vitamin D encouraged scientists to divide seasonal models into non-classical climate seasons and seasons with average level of vitamin D [10]. According to our research, there is a slight correlation between frequency of MS recurrences and climate factors having seasonal variabilities.

Statistical analysis of data did not show any differences in frequency of disease relapses due to sex – mean annualized relapse rate (ARR) was 0.39 for men and 0.39 for women of all age groups during 4 years.

But more detailed analysis of age groups showed that recurrence rate of MS for men aged 20-39 years was 0.48, and for women – 0.37; men aged 40-49 years – 0,21; women aged 40-49 – 0,42; women aged after 50 years – 0.66 and men aged after 50 years – 0,13 (Fig. 4).

Relationship between duration of the disease and MS relapses was weak-positive (0.24, p<0.001) in males. Average negative correlation by age (-0.37, p<0.001) was detected between the onset of the disease and the incidence of MS recurrence in males (this may also be associated with the rate of progression in men requiring further investigation). We did not observe this connection in women. Thus, frequency of MS recurrences gradually decreases by 2.5 times in adult males comparing to young ones (however, these data may be related to small number of male patients in this age category); frequency of exacerbations in women is kept at relatively stable level approximately to the age of 50 years. There is increase in frequency of exacerbations by 2 times at the age of menopause. The distribution of ARR is shown in Fig. 5.
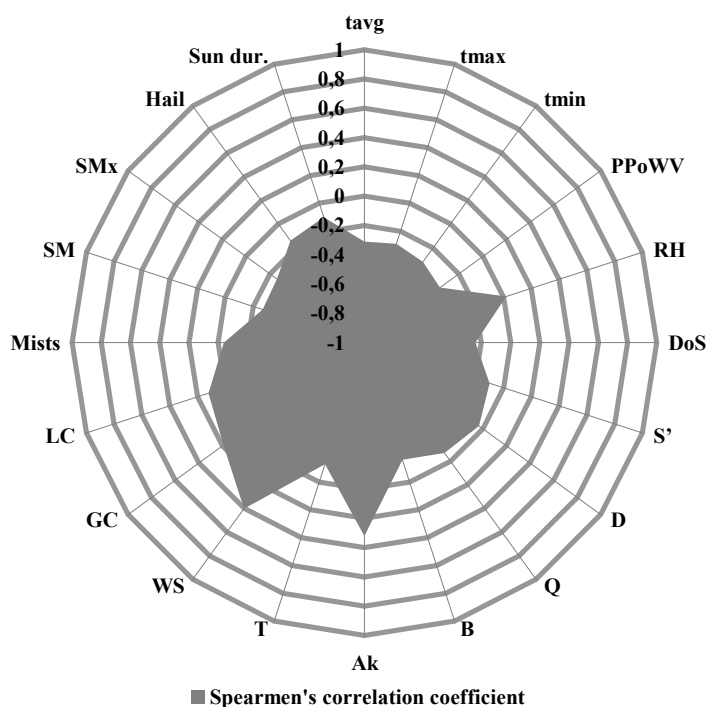
Fig. 3. Spearmen's correlation between the proposed climatic factors and the frequency of exacerbations of MS

We assume that occurrence of distinctive patho-logical mechanisms of relapses in men and women is different, which coincides with results of other studies. Results of other large-scale studies also suggest that hormonal status, having dynamic throughout life, is one of the most important factors influencing duration of the disease and frequency of recurrences [12]. Incidences of relapses increase significantly in women with age. This is probably due to a sharp decrease in the level of sex hormones in the postmenopausal period [6]. Lowered levels of sex hormones quite often is the consequence of MS. MRI revealed presence of pathological basis for the existence of different clinical course of MS: women have more expressed inflammatory processes but less destructive foci than men [15].
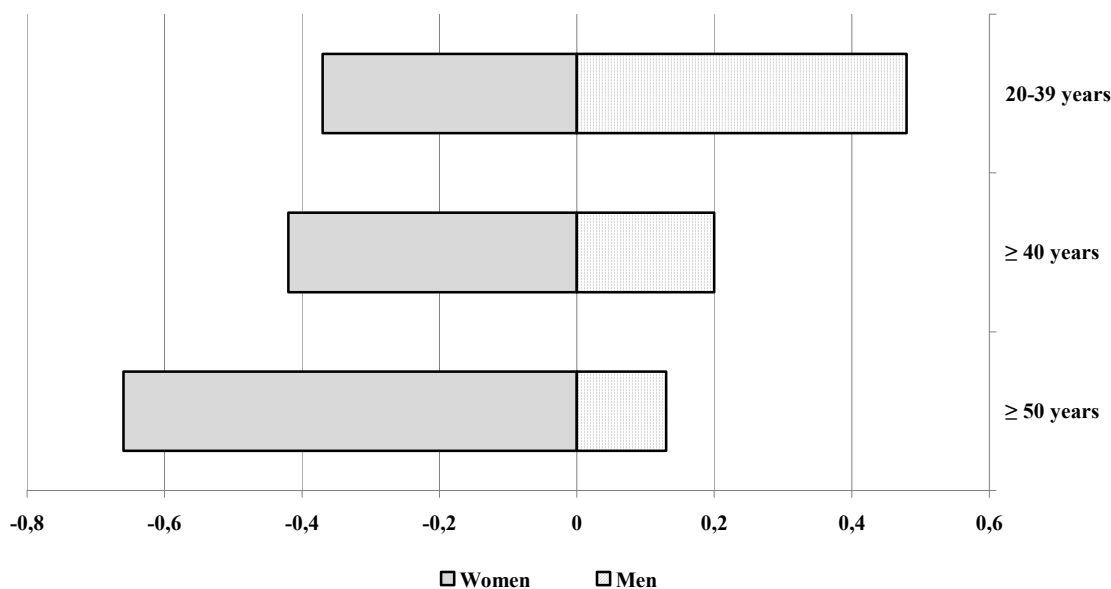

Fig. 4. Annual relapse rate per age groups between men and women
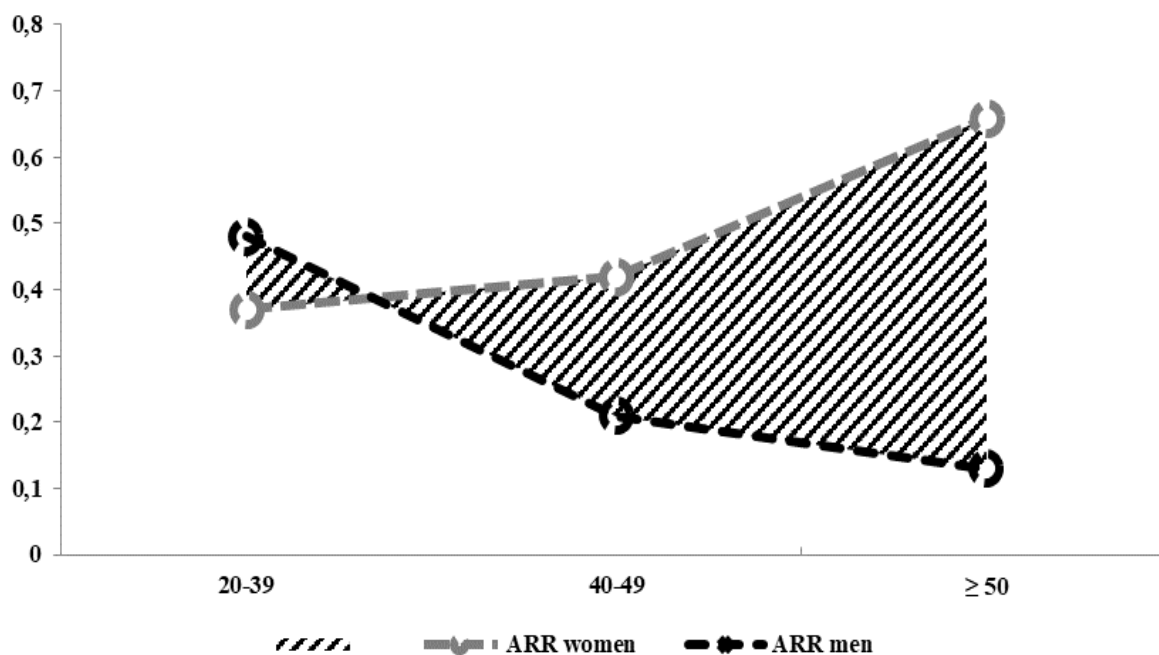
Fig. 5. Annualized relapse rate in women and men of different age groups during a 4-year observation period

Testosterone acts only as a neuroprotector of general action not affecting the focus of MS on MRI; oestriol improves the picture of MRI confirming hypothesis of its effect in demyelination processes. This is associated with higher incidence of exacerbations in men aged up to 40 years compared to men over 40 years of age [14]. It is opposite in women. Features of chronometric indices just follow dynamics of hormonal status throughout life. Testosterone itself is a positive hormone in the aspect of MS [15]. However, it has insignificant effect on demyelinization mechanism. It serves as a suppressing mediator at the onset of the disease, as it causes a cerebrovascular anti-inflammatory effect not affecting destruction site. Estrogen does not have this action. It affects the median stage of pathogenesis – demyelinization as it acts on those cells in pathogenesis chain which start detecting their activity only in the presence of pathological process [14, 15]. Both testosterone and estrogen control the level of relapse. And only estrogen does not allow disease; to progress its influence on lesions in MS is confirmed on MRI, explaining lower prevalence of progressive course in women [14]. Our investigation covers significant issues concerning sexual dimorphism of MS, which are not well understood.

In conclusion, the incidence of relapses in MS can be explained by combination of seasonal factors, distinctive hormonal status, determined anatomical and physiological gender peculiarities.

CONCLUSIONS

1. Episodes of MS relapses in both genders prevailed in winter-spring period. The single cases of exacerbations were recorded in summer, especially low rate of relapses was observed during summer in men. Multiple regression model including suggested climate factors showed multiple correlation coefficient – 0.55 (p<0.01).

2. The prevalence of MS relapse rate in different age groups differs: the rate of recurrences increases in women aged after 50 years (mean annual relapse rate (ARR) = 0.66), while it slowly decreases in men with aging.

3. The duration of the disease did not have significant effect on the course of MS in women, whereas a weak negative relationship between the duration of the disease and the frequency of MS in men was showed. Correspondingly, the average negative correlation was detected between the age of disease onset and the incidence of MS recurrence in males, while this correlation was not observed in females.

4. We suggested that recurrence of MS is a result of multifactorial influence of combination of external and internal factors.

Conflicts of interest: The authors declare no conflict of interest.

REFERENCES

1. Nikolenko OO, Shulga OD, Kozliuk VV, Valetska UV, Tenderiak OV Zheshko OM, Dubinets MI, Yurko OA. [Influence of seasonal climatic factors on the frequency of exacerbations of multiple sclerosis]. Ukrayinskyi medychnyi chasopys. 2019;2(2):130. doi: https://doi.org/10.32471/umj.1680-3051.130.140263

2. Halik OI, Basyuk TO. Method instructions. Ukrainian Climate Reference. Available from: http://ep3.nuwm.edu.ua/591/1/01-03-16.pdf

3. Zheshko OM, Shulga OD, Dubinets MI, Yurko OA, Lopachak OR. [Exacerbation of multiple sclerosis: a clinical and paraclinic paradox]. Prykarpatskyi visnyk NTSH. Puls. 2019;5(57):65-69. doi: https://doi.org/10.21802/2304-7437-2019-5(57)-65-69

4. Nefodov OO, Mamchur VY. [Experimental allergic encephalomyelitis: features of analgesic therapy and the place of anticonvulsants as analgesics]. Medicni perspektivi. 2015;(20)4:4-9 Available from: http://nbuv.gov.ua/UJRN/Mp_2015_20_4_3. Ukrainian. doi: https://doi.org/10.26641/2307-0404.2015.4.56125.

5. Central geophysical observatory named after Boris Sreznevsky. Available from: http://cgo-sreznevskyi.kiev.ua/

6. Bouman A, Heineman MJ, Faas MM. Sex hormones and the immune response in humans. Human Reproduction 2005;11(4):411-23. doi: https://doi.org/10.1093/humupd/dmi008

7. Bove R., Gilmore W. Hormones and MS: Risk factors, biomarkers, and therapeutic targets. Multiple Sclerosis Journal. 2018;24(1):17-21. doi: https://doi.org/10.1177/1352458517737396

8. Chitnis T. The role of testosterone in MS risk and course. Multiple Sclerosis Journal. 2018;24(1):36-41. doi: https://doi.org/10.1177/1352458517737395

9. Damasceno A, Glehn FV, de Deus-Silva L, Damasceno BP. Monthly variation of multiple sclerosis activity in the southern hemisphere: analysis from 996 relapses in Brazil. Eur J Neurol. 2012;19(4):660-2. doi: https://doi.org/10.1111/j.1468-1331.2011.03543.x

10. Vojinovic Slobodan, Savic Dejan, Lukic Stevo, Savic Ljiljana, Vojinovic Jelena. Disease relapses in multiple sclerosis can be influenced by air pollution and climate seasonal conditions. Vojnosanitetski pregled. 2014;72:30-30. doi: https://doi.org/10.2298/VSP140121030V

11. Dunn SE, Lee H, Pavri FR, Zhang MA. Sex-Based Differences in Multiple Sclerosis (Part I): Biology of Disease Incidence. Current Topics in Behavioral Neurosciences. Springer. 2015;26:29-56. doi: https://doi.org/10.1007/7854_2015_371

12. Gomez FP, Steelman AJ, Young CR, Welsh CJ. Hormone and immune system interactions in demyelinating disease. Hormones and Behavior. 2013;63(2):315-21. doi: https://doi.org/10.1016/j.yhbeh.2012.10.014

13. Hartl C, Obermeier V, Gerdes LA, Brügel M, von Kries R, Kümpfel T. Seasonal variations of 25-OH vitamin D serum levels are associated with clinical disease activity in multiple sclerosis patients. Journal of the Neurological Sciences. 2017;375:160-4. doi: https://doi.org/10.1016/j.jns.2017.01.059

14. Tomassini Valentina, Onesti Emanuela, Mainero Caterina, Giugni E, Paolillo Andrea, Salvetti Massimo, Nicoletti Ferdinando, Pozzilli C. Sex hormones modulate brain damage in multiple sclerosis: MRI evidence. Journal of neurology, neurosurgery, and psychiatry. 2005;76:272-5. doi: https://doi.org/10.1136/jnnp.2003.033324

15. Sicotte NL, Giesser BS, Tandon V, et al. Testosterone treatment in multiple sclerosis: A pilot study. Arch Neurol 2007;64:683-8. doi: https://doi.org/10.1001/archneur.64.5.683

СПИСОК ЛІТЕРАТУРИ

1. Вплив сезонних кліматичних чинників на частоту загострень розсіяного склерозу / О. О. Ніколенко та ін. *Укр. мед. часопис.* 2019. Т. 130, № 2. ІІІ/ІV. DOI: https://doi.org/10.32471/umj.1680-3051.130.140263

2. Галік О. І., Басюк Т. О. Довідкові дані з клімату України: метод. вказівки. Рівне: НУВГП, 2014. 158 с. URL: http://ep3.nuwm.edu.ua/591/1/01-03-16.pdf

3. Загострення розсіяного склерозу: клініко – параклінічний парадокс / О. М. Жешко та ін. *Прикарпат. вісник НТШ. Пульс.* 2019. Т. 57, № 5). С. 65-69. DOI: https://doi.org/10.21802/2304-7437-2019-5(57)-65-69

4. Нефьодов О. О., Мамчур В. Й. Експериментальний алергічний енцефаломієліт: особливості знеболюючої терапії та місце антиконвульсантів у якості анальгетиків. *Медичні перспективи.* 2015. Т. 20, № 4. С. 4-9. URL: http://nbuv.gov.ua/UJRN/Mp_2015_20_4_3. DOI: https://doi.org/10.26641/2307-0404.2015.4.56125

5. Центральна геофізична обсерваторія імені Бориса Срезневського. URL: http://cgo-sreznevskyi.kiev.ua/

6. Bouman A., Heineman M. J., Faas M. M. Sex hormones and the immune response in humans. *Human Reproduction Update.* 2005. Vol. 11, No. 4. P. 411-423. DOI: https://doi.org/10.1093/humupd/dmi008

7. Bove R., Gilmore W. Hormones and MS: Risk factors, biomarkers, and therapeutic targets. *Multiple Sclerosis Journal.* 2018. Vol. 24, No. 1. P. 17-21. DOI: https://doi.org/10.1177/1352458517737396

8. Chitnis T. The role of testosterone in MS risk and course. *Multiple Sclerosis Journal.* 2018. Vol. 24, No. 1. P. 36-41. DOI: https://doi.org/10.1177/1352458517737395

9. Damasceno A., Glehn F. V., de Deus-Silva L., Damasceno B. P. Monthly variation of multiple sclerosis activity in the southern hemisphere: analysis from 996 relapses in Brazil. *Eur. J. Neurol.* 2012. Vol. 19, No.4. P. 660-662. DOI: https://doi.org/10.1111/j.1468-1331.2011.03543.x

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

conditions / S. Vojinovic et al. *Vojnosanitetski pregled.* 2014. Vol. 72. P. 30-30.
DOI: https://doi.org/10.2298/VSP140121030V

11. Dunn S. E., Lee H., Pavri F. R., Zhang M. A. Sex-Based Differences in Multiple Sclerosis (Part I): Biology of Disease Incidence. Current Topics in Behavioral Neurosciences. *Springer.* 2015. Vol. 26. P. 29-56. DOI: https://doi.org/10.1007/7854_2015_371

12. Gomez F. P., Steelman A. J., Young C. R., Welsh C. J. Hormone and immune system interactions in demyelinating disease. *Hormones and Behavior.* 2013. Vol. 63, No. 2. P. 315-321.
DOI: https://doi.org/10.1016/j.yhbeh.2012.10.014

13. Seasonal variations of 25-OH vitamin D serum levels are associated with clinical disease activity in multiple sclerosis patients / C. Hartl et al. *Journal of the Neurological Sciences.* 2017. Vol. 375. P. 160-164. DOI: https://doi.org/10.1016/j.jns.2017.01.059

14. Sex hormones modulate brain damage in multiple sclerosis: MRI evidence / V. Tomassini et al. *J. neurology, neurosurgery, and psychiatry.* 2005. Vol. 76. P. 272-275. DOI: https://doi.org/10.1136/jnnp.2003.033324

15. Sicotte N. L., Giesser B. S., Tandon V. Testosterone treatment in multiple sclerosis: A pilot study. *Arch Neurol.* 2007. Vol. 64. P. 683-688.
DOI: https://doi.org/10.1001/archneur.64.5.683

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THE CONTENT OF CYTOKINES IN THE BLOOD SERUM OF PATIENTS WITH EARLY LATENT SYPHILIS IN PROCESS OF TREATMENT

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Abstract. The content of cytokines in the blood serum of patients with early latent syphilis in process of treatment. Zakharov S.V., Zakharov V.K., Gorbuntsov V.V. *Objective – to study the concentration of pro- and anti-inflammatory cytokines in patients with early latent syphilis before and after treatment. The study was conducted in 112 patients with early latent syphilis (52 men and 60 women) and 15 healthy persons of the control group – all aged 18-43. Serological tests were used: the classical complex of serological reactions (CSR), ELISA, the reaction of passive hemagglutination (RPGA), immunofluorescence reaction with absorption (RIF-abs) and RIF-200. Using ELISA, the levels of cytokines IL-2, IL-6, IL-10, TNFα, and INFγ were determined in serum (in patients with latent syphilis, before and after treatment). The analysis of the received data was carried out with application of the program package Statistics 6.0. To identify the relationships between the indices, Friedman's nonparametric variance analysis with the*