ORIGINAL ARTICLE

High incidence of multiple sclerosis in the Republic of Karelia: is there effect of cold?

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Abstract

OBJECTIVE: This study was aimed at estimating the multiple sclerosis (MS) incidence rate in the Republic of Karelia in respect with its geographical environment as a region or European North of Russian Federation (RF) in comparison with other regions of the European part of RF.

MATERIAL & METHODS: Medical database including outpatient and inpatient cards, hospital discharge summaries of patients with MS who were treated at the Karelian Republican Hospital in the period 2013-2019 for MS was analyzed. Rate of the total and primary MS morbidity was calculated. The rates of MS morbidity in regions of European part of RF were collected from the published open sources.

RESULTS: MS incidence rate in Karelia for the analyzed time period was 65,1 per 100,000 population, what is regarded as the high risk of MS. The primary MS morbidity was 2,7 ± 0,5 per 100,000 population in average. The MS incidence in Karelia proved higher than those in southern regions of the European part of RF. Higher prevalence of MS morbidity in the North of RF is indicative of a global, presumably climatic, factor which drives MS morbidity.

CONCLUSION: The results obtained demonstrate that geographical environment including low environmental temperature indeed contributes to the MS incidence. Higher prevalence of MS morbidity in the North is in good line with earlier reported hypersensitivity of patients with MS to cold. Thus, further investigations based on cold environmental stress prevention in MS patients are needed to find more effective approaches for disease monitoring.

Abbreviations:
Multiple sclerosis (MS); Russian Federation (RF).

Introduction

Multiple sclerosis (MS) is known as one of the most common neurological diseases in young adults. Pathogenic mechanisms of MS include autoimmune inflammatory and neurodegenerative processes leading to multifocal and diffuse lesions of the central nervous system (Davis *et al.* 2018; GBD 2016 Multiple Sclerosis Collaborators 2019; Kurtzke 1993; Schmidt & Jahno 2016). MS has multifactorial origin that includes environmental, exogenous, and genetic factors (GBD 2016 Multiple Sclerosis Collaborators 2019; Schmidt & Jahno 2016; Waubant *et al.* 2019). Climatic and geographical factors are supposedly responsible for the global distribution of the MS morbidity (GBD 2016 Multiple Sclerosis Collaborators 2019; Schmidt & Jahno 2016; Vojinović *et al.* 2015; Waubant *et al.* 2019). Geographically, MS distribution has three clear zones: with high risk of MS morbidity (number of MS cases per 100,000 population) which corresponds to the annual incidence rate over 30, medium risk – to 5-30, and low risk – to less than 5 (Kurtzke 1993). Correspondingly, high rate of MS appears the characteristic for regions with cold and humid climate. Such association of MS morbidity with region and seasonal dynamics was documented in several studies (Benjaminse *et al.* 2014; GBD 2016 Multiple Sclerosis Collaborators 2019; Kurtzke 1993; Schmidt & Jahno 2016; Vojinović *et al.* 2015).

Most of European states are relatively uniform and not so big by size, and therefore present no distinct latitude differences in climate. Even larger states with significant longitudinal extent, like Sweden or Norway, cannot be taken into analysis because they entirely locate in Northern latitudes. The Russian Federation (RF), in this respect, would present a unique example of extension from North to South (cal. 3000 km), from subtropics to arctic zone. In RF, the annual incidence rate of MS ranges from 25 to 70 cases per 100,000 population, and most regions of the RF refer to the zone of medium MS risk (Schmidt & Jahno 2016; Gusev *et al.* 2002). Over the past years, an increase in the incidence of MS was documented in many regions of the RF. This dynamics is supposedly associated both with a real increase of the incidence of MS, and with improved diagnostics and treatment of MS according to the standards and clinical guidelines set by the Ministry of Health of the RF (Gusev *et al.* 2002; Schmidt & Jahno 2016). The sophisticated diagnostic techniques both for early detection of MS and differential diagnosis of demyelinating diseases were implemented through the use of high-field MRI and modern laboratory diagnostic techniques. Additionally, all provinces of RF utilize unified standards for diagnostics of MS what is beneficial for analysis.

The territory of the Republic of Karelia is located in the North-West of RF. In the year 2019 its population was 618,100 people (The Republic of Karelia in figures'2019 2019). The climate of Karelia is considered as a kind of cold climate and combines the characteristics of both the moderate continental and marine climate (Gromcev *et al.*. 2019; Keller & Kuvakin 1998). In addition to the low average annual temperature, the climatic conditions of Karelia are characterized by low sun exposure and marked photoperiodism, which are considered as environmental risk factors for MS (Benjaminse *et al.* 2014; GBD 2016 Multiple Sclerosis Collaborators 2019; Vojinović *et al.* 2015).

Low-temperature environment is currently supposed to be one of notable factors that influence the MS morbidity. In our earlier studies we have reported on high sensitivity of MS patients to cold seen as so-called cold-associated symptoms and discomfort (Gerasimova-Meigal & Sirenev 2017, 2018). We also found that MS morbidity in Karelia has almost doubled for the last years from 24,9 per 100,000 population in 2005 (Gusev & Ivanova 2005) to 61,2 in 2019 (Sirenev *et al.* 2019). Correspondingly, MS morbidity risk in Karelia shifted from the medium to high risk according Kurtzke scale (Kurtzke 1993).

Then a question comes: How this increase of MS incidence in Karelia corresponds with the all-Russian tendency? As such, this study was aimed to estimate the MS incidence rate in the Republic of Karelia in respect with its geographical environment, in comparison with other regions of the European part of RF.

Materials & Methods

Medical database of patients who were treated at the Karelian Republican Hospital in the period 2013-2019 for MS was analyzed. The diagnosis of MS was verified in accordance with the standards and practices of health care in the profile "neurology" adopted in the RF (Neurology: Health Care Standards 2017). Considering the endemicity of the Republic of Karelia on tick-borne encephalitis and borreliosis, diagnosis of MS included also serological tests to exclude these specific infections. Outpatient and inpatient cards, and hospital discharge summaries were the source documents. The total number of patients, their age, gender, duration of the disease, primary morbidity, and the age of MS debut were estimated. Rates of the total and primary MS morbidity were calculated per investigated year. Descriptive statistics, such as mean and its standard deviation, were assessed.

The rates of MS morbidity in regions of European part of RF were collected from published open sources, arranged and averaged in respect with the Federal Districts structure of RF.

Results

According to medical database, in 2019 in the Republic of Karelia, 401 patients with a reliably ascertained diagnosis of MS were supervised. Thus, the MS incidence rate in Karelia for 2019 was estimated as 65,1 per 100,000 population. The age of patients with MS ranged from 19

to 73 years (mean age 46,2 ± 12,23 years). The gender distribution of MS patients was as follows: 256 women (63,8%) and 145 men (36,2%). The disease duration ranged from 1 to 46 years (12,4 ± 9,3 years in average).

Within the time period from 2013 to 2019 in Karelia, the diagnosis of MS was reliably ascertained for 120 *de novo* patients. According to our estimations, annually in the Republic of Karelia MS was diagnosed in 13-20 new patients. The primary MS morbidity averaged 2,7±0,5 per 100,000 population, and the average debut age of the disease was 33,7±7,5 years.

The MS incidence rate in Karelia and some regions of the European part of RF is presented in the table 1 and figure 1. The table 1 shows that MS incidence rate and, correspondingly, the MS risk in regions located in northern high and middle latitudes (Northwestern, Central and Volga Federal Districts,) is greater than that in the most southern regions of the European part of RF (Southern and North Caucasus Federal Districts). Figure 1 shows the same data in the time-dependent manner. It is seen that in all RF regions, MS morbidity was systematically growing. Still, higher prevalence of MS morbidity in the North of RF was the characteristic over the studied time. This is indicative of a global, presumably climatic, factor independent of such non-climatic factors, as economic situation and health care quality, which drives MS morbidity.

Discussion

In comparison to the study of Gusev & Ivanova (2005) over the past years MS morbidity in the Republic of Karelia has doubled (Sirenev *et al.* 2019). This allows consider the present rating of MS morbidity in Karelia as a high risk zone of MS (Gusev *et al.* 2002; Kurtzke 1993; Schmidt & Jahno 2016). The gender-age structure

Tab. 1. Multiple sclerosis incidence rate in the European part of Russian Federation

The region of Russian Federation	Annual MS incidence rate (number of cases per 100,000 population)[1]	MS risk[2] (Kurtzke 1993)
Northwestern Federal District	24,9 (21,0; 55,0)	
Saint-Petersburg, Leningrad and Pskov regions (Gusev *et al.* 2002)	55,0	High
Republic of Karelia (Gusev & Ivanova 2005; Sirenev *et al.* 2019)	24,9; 61,2	Medium / high
Kaliningrad region (Gusev *et al.* 2002)	21,0	Medium
Komi Republic (Gusev *et al.* 2002)	16,1	Medium
Central Federal District	51,4 (37,8; 54,7)	
Kursk region (Laskov *et al.* 2017)	78,4	High
Smolensk region (Pysina *et al.* 2009)	55,4	High
Kaluga region (Maslova *et al.* 2017)	54,7	High
Moscow (Bojko *et al.* 2013)	53,3	High
Moscow region (Kotov *et al.* 2012)	37,8	High
Vladimir region (Gusev *et al.* 2002)	51,4	High
Bryansk region (Jurchenko *et al.* 2015)	47,9	High
Kostroma region (Gusev *et al.* 2002)	35,0	High
Tambov region (Gusev *et al.* 2002)	28,5	Medium
Volga Federal District	33,7 (31,4; 38,7)	
Samara region (Gusev *et al.* 2002)	42,4	High
Republic of Tatarstan (Habirov *et al.* 2013)	42,1	High
Republic of Bashkortostan (Bahtijarova *et al.* 2014; Ivanova *et al.* 2017; Zhelnin *et al.* 2008)	35,3-46,5	High
Republic of Mordovia (Gusev *et al.* 2002)	34,3	High
Ulyanovsk region (Gusev *et al.* 2002)	33,7	High
Nizhny Novgorod region (Zhelnin *et al.* 2008)	32,8	High
Kirov region (Gusev *et al.* 2002)	31,8	High
Chuvash Republic (Zhelnin *et al.* 2008)	26,0-31,0	Medium / high
Saratov region (Gusev *et al.* 2002)	27,2	Medium
Southern Federal District	18,9 (15,9; 24,4)	
Rostov region (Bahtijarova *et al.* 2014)	29,8	Medium
Krasnodar region (Strelnikova *et al.* 2014)	18,9	Medium
Republic of Adygea (Gusev *et al.* 2002)	12,9	Medium
North Caucasus Federal District	14,7 (13,3; 18,9)	
Stavropol region (Potapova *et al.* 2014)	20,0-32,8	Medium / high
Republic of Kabardino-Balkaria (Zikhova *et al.* 2013)	13,7	Medium
Republic of North Ossetia (Gusev *et al.* 2002)	15,7	Medium
The Republic of Ingushetia (Goncharova & Uzhahov 2017)	13,2	Medium
The Republic of Dagestan (Magomedov *et al.* 2009)	5,7	Medium

[1] - data averaged for Federal District are presented in a format Median (0.25; 0.75).
[2] - High - annual incidence rate over 30, Medium – 5-30, and Low – below 5, according to Kurtzke (1993).

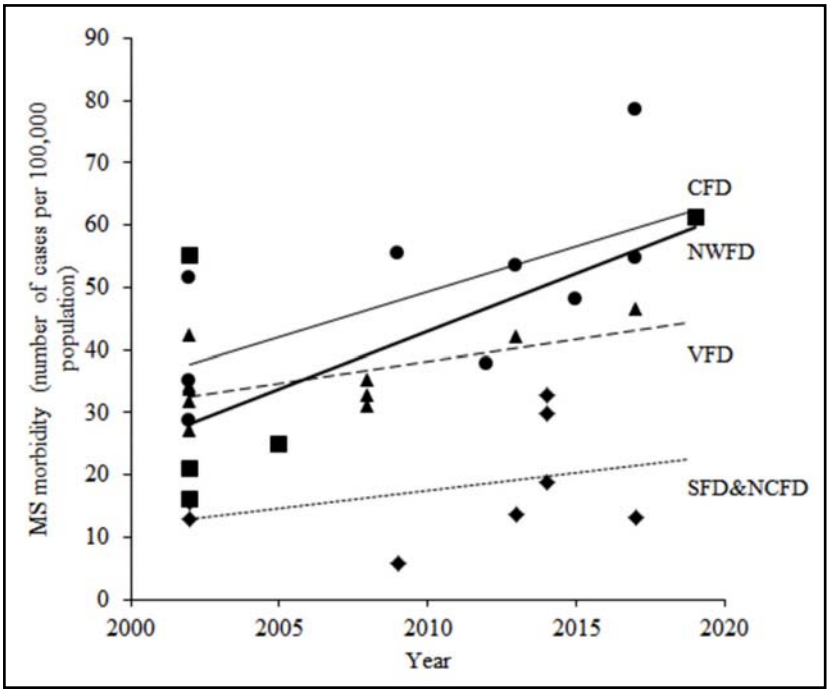

Fig. 1. The dynamics of Multiple sclerosis incidence rate in the European part of Russian Federation.

■ ——— NWFD, Northwestern Federal District

▲ ——— CFD, Central Federal District

● — — — VFD, Volga Federal District

♦ ····· SFD&NCFD, Southern Federal District & North Caucasus Federal District

of the MS morbidity in Karelia, high rate of the disease among young people, mainly among women, was typical of overall MS distribution (GBD 2016 Multiple Sclerosis Collaborators 2019; Gusev *et al.* 2002; Schmidt & Jahno 2016; Waubant *et al.* 2019).

Presently, the MS morbidity in Karelia is higher than that in most southern parts of RF (see table 1). The table 1 shows that in the European part of the RF, the annual incidence of MS depends on the latitude of the region, and corresponds to the "north-south" gradient of the MS distribution (Benjaminse *et al.* 2014; GBD 2016 Multiple Sclerosis Collaborators 2019; Gusev *et al.* 2002; Kurtzke 1993; Schmidt & Jahno 2016; Vojinović *et al.* 2015). As MS morbidity is also dependent on various exogenous factors including the environmental pollution (GBD 2016 Multiple Sclerosis Collaborators 2019; Gusev *et al.* 2002; Schmidt & Jahno 2016; Waubant *et al.* 2019), the high rate of MS in large industrial cities might partially impaired the latitudinal pattern of distribution of the incidence of MS.

Thus, the geographical characteristic of the territory, e.g. latitude, is still believed to be one of crucial environmental etiological factors of MS. In higher latitudes, low sun exposure and, subsequently, lower vitamin D status is considered as the most significant of these factors (GBD 2016 Multiple Sclerosis Collaborators 2019; Waubant *et al.* 2019). Vitamin D supplementation programs presented good outcome in prevention of MS onset in northern European states (Waubant *et al.* 2019). For that reason, the effect of environmental temperature, especially, cold exposure, is still underestimated. However, along with the sun exposure, environmental temperature also appears essential level for latitude-dependent characteristics of climate (Keller & Kuvakin 1998). Well-known phenomenon of heat intolerance in MS patients, or Uhthoff's phenomenon (Davis *et al.* 2018; Schmidt & Jahno 2016), surprisingly does not correlate with low MS morbidity in states with warmer climate. By contrast, our data on the epidemiology of MS in Karelia are in a good line with our earlier results on the hypersensitivity of patients with MS to cold (Gerasimova-Meigal & Sirenev 2017; 2018). Additionally, cold-induced stress in human's daily activities is not so readily controlled and prevented, unlike to sun exposure and vitamin D supplementation.

Conclusion

Thus, the MS incidence rate in the Republic of Karelia for the period 2013–2019 at the level of 65,1 per 100,000 population was found to correspond to a high risk zone for this disease (GBD 2016 Multiple Sclerosis Collaborators 2019; Gusev *et al.* 2002; Kurtzke 1993; Schmidt & Jahno 2016). MS incidence in Karelia was higher than

that in most southern parts of RF, what is in a good line with our earlier finding of high sensitivity to cold in MS patients (Gerasimova-Meigal & Sirenev 2017; 2018). This demonstrates that cold environment indeed contributes to the MS incidence. Thus, further investigations are needed to discover the effects of climatic factors on the course and the mechanisms of MS development, as well as to find more effective approaches for disease prevention and treatment.

Limitations and further prospective

Some important data on MS incidence from the most northern European RF regions, for example Murmansk, Archangelsk and Nenets autonomous region, located to the north of Karelia, were not available from the open sources. In future studies we suppose to include these data into analysis. Also, some regions from the North-West Federal District are actually located at the same latitude with those of the Central Federal District. Additionally, we anticipate some effect of the Covid-19 pandemic on the MS epidemiology due to its inflammatory and immunological effects. As such, the post-pandemic data must be further analyzed.

Conflict of Interests

The authors declare no conflict of interest in this study.

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REFERENCES

1 Bahtiiarova KZ, Goncharova ZA (2014). Rassejannyj skleroz v Respublike Bashkortostan i Rostovskoj oblasti: sravnitel'naja epidemiologicheskaja harakteristika [(Multiple sclerosis in the Republic of Bashkortostan and the Rostov region: a comparative epidemiological study.) (In Russian with English abstract.)] *Zh Nevrol Psikhiatr im S S Korsakova.* **114**(2 Pt 2): 5–9.

2 Benjaminse E, Olavsen J, Karlberg M, Alstadhaug KB. (2014). Multiple sclerosis in far north – incidence and prevalence in Nordland County, Norway, 1970-2010. *BMC Neurol*. **14**(1): 226. DOI: 10.1186/s12883-014-0226-8.

3 Bojko AN, Kukel TM, Lysenko MA, Vdovichenko TV, Gusev EI (2013). Klinicheskaja epidemiologija rassejannogo skleroza v Moskve. Opisatel'naja epidemiologija na primere populjacii odnogo iz okrugov goroda [(Clinical epidemiology of multiple sclerosis in Moscow. Discriptive epidemiology in population of one region of Moscow) (In Russian with English abstract.)] *Zh Nevrol Psikhiatr im S S Korsakova.* **113**(10 Pt 2): 8–14.

4 Davis SL, Jay O, Wilson, TE (2018). Thermoregulatory dysfunction in multiple sclerosis. *Handbook of clinical neurology.* **157**: 701–714. https://doi.org/10.1016/B978-0-444-64074-1.00042-2

5 GBD 2016 Multiple Sclerosis Collaborators (2019). Global, regional, and national burden of multiple sclerosis 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* **18**(3): 69–285. DOI: https://doi.org/10.1016/S1474-4422(18)30443-5.

6 Gerasimova-Meigal LI, Sirenev IM (2017). Holod-inducirovannaja reaktivnost' u pacientov s rassejannym sklerozom. [(Cold-induced reactivity in patients with multiple sclerosis.) (In Russian with English abstract.)] *Pathol Physiol Exp Ther.* **61**: 56–62. doi https://doi.org/10.25557/0031-2991.2017.03.56-62.

7 Gerasimova-Meigal LI, Sirenev IM (2018). Pathogenic role of autonomic dysfunction in cold intolerance in multiple sclerosis patients. *Pathophysiol.* **25**(3): 196.

8 Goncharova ZA, Uzhakhov RM (2017). Analiz rasprostranennosti i faktory riska razvitija rassejannogo skleroza v Respublike Ingushetija [(An analysis of the prevalence and risk factors for multiple sclerosis in the Republic of Ingushetia.) (In Russian with English abstract.)] *Zh Nevrol Psikhiatr im S S Korsakova.* **117**(2 Vyp. 2): 6–9. doi: 10.17116/jnevro2017117226-9.

9 Gromcev AN, Kuznecov OL, Shkiperova GT, editors (2019). Gosudarstvennyj doklad o sostoyanii okruzhayushchej sredy Respubliki Kareliya v 2018 g [(State Report on the State of the Environment of the Republic of Karelia in 2018.) (In Russian)]. Petrozavodsk: Ministry of Natural Resources and Ecology of the Republic of Karelia, ISBN 978-5-9631-0749-2, p. 314.

10 Gusev EI, Zavalishin IA, Bojko AN, Khoroshilova NL, Iakovlev AP. (2002). Epidemiologicheskie harakteristiki rassejannogo skleroza v Rossii. [(Epidemiological characteristics of multiple sclerosis in Russia.) (In Russian with English abstract.)] *Zh Nevrol Psikhiatr im S S Korsakova.* Suppl.: 3–6.

11 Gusev VA, Ivanova GYu (2005). Epidemiologija rassejannogo skleroza v Respublike Karelija. [(Epidemiology of multiple sclerosis in the Republic of Karelia.) (In Russian with English abstract.)] *Med Akad Zh.* **5**(2-6): 250–252.

12 Ivanova EV, Bakhtiyarova KZ, Safronova EV (2017). Mediko-social'naya harakteristika bol'nyh rasseyannym sklerozom v Ufe [(Medico-social characteristic of patients with multiple sclerosis in Ufa.) (In Russian with English abstract.)] *Med-Soc Expert Reabil (Medical and Social Expert Evaluation and Rehabilitation, Russian Journal).* **20**(4): 181–184. (In Russ.). DOI: http://dx.doi.org/10.18821/1560-9537-2017-20-4-181-184

13 Jurchenko AN, Jurchenko JuN, Smagina IV (2015). Epidemiologiya rasseyannogo skleroza v Bryanskoj oblasti [(Epidemiology of Multiple Sclerosis in the Bryansk Region.) (In Russian with English abstract.)] *Zh Nevrol Psikhiatr im S S Korsakova.* **115**(8 Pt 2): 91–92.

14 Keller AA, Kuvakin VI. (1998). Medicinskaya ekologiya [(Medical ecology.) (In Russian)]. SPb: "Petrograd and Co.", ISBN 5-88143-050-6, p. 256.

15 Khabirov FV, Babicheva NN, Esin RG, Kochergina OS, Granatova EV, Khaybullin TI (2013). Klinicheskaya i social'no-demograficheskaya harakteristika rasseyannogo skleroza v Respublike Tatarstan. [(The Clinical and epidemiological data in patients with of multiple sclerosis of the Republic of Tatarstan.) (In Russian with English abstract.)] *Prakticheskaja medicina.* **68**(1 Pt 1): 15–18.

16 Kotov SV, Iakushina TI, Lizhdvoĭ VIu (2012). Kliniko-epidemiologicheskie aspekty rasseyannogo skleroza v Moskovskoj oblasti [(Clinical and epidemiological aspects of multiple sclerosis in the Moscow region.) (In Russian with English abstract.)] *Zh Nevrol Psikhiatr im S S Korsakova.* **112**(3): 60–62.

17 Kurtzke JF (1993). Epidemiologic evidence for multiple sclerosis as an infection. *Clin Microbiol Rew.* **6**(4): 382–427. DOI: 10.1128/CMR.6.4.38.

18 Laskov VB, Logacheva EA, Tretyakova EE, Gridnev MA (2017). [(Clinical and epidemiological features of patients with multiple sclerosis in the Kursk Region.) (In Russian with English abstract.)] *Nevrol Neuropsiciatr Psycosomat (Neurology, neuropsychiatry, psychosomatics).* **9**(1): 55–60. DOI: http://dx.doi.org/10.14412/2074-2711-2017-1-55-60.

19 Magomedov MM, Halitov IA, Mihajlova BI, Tidulaeva PR, Kojchakaeva AS, Malikova AG et al. (2009). Rasseyannyj skleroz v Dagestane [(Multiple Sclerosis in Dagestan.) (In Russian)] *Fundamental'nye issledovanija.* **9**: 51–52.

20 Maslova NN, Andreeva EA, Belyy YuA, Yerokhina EV (2014). Kliniko-epidemiologicheskie i nejrooftal'mologicheskie osobennosti bol'nyh rasseyannym sklerozom na primere Kaluzhskoj oblasti.) [(Clinical, epidemiological and neuro-ophthalmological features of patients with multiple sclerosis: study of Kaluga region.) (In Russian with English abstract.)] *Ann Klin Exp Neurol.* **8**(3): 30–37.

21 Potapova IG, Didenko NN, Denisjuk VV, Karpov SM (2014). Aktual'nye voprosy rasprostranennosti rasseyannogo skleroza v Stavropol'skom krae. [(Current issues of the prevalence of multiple sclerosis in the Stavropol region.) (In Russian)]. *Usp Sovrem Estestvozn.* **6**: 126–128.
22 Pysina AM (2009). Kliniko-epidemiologicheskie osobennosti rasseyannogo skleroza v Smolenskoj oblasti [(Clinical and epidemiological features of multiple sclerosis in the Smolensk region.) (In Russian)]. *Vestn Smolensk Gos Med Akad.* **2**: 73–74.
23 Respublika Kareliya v cifrah'2019: kratkij statisticheskij sbornik [(The Republic of Karelia in figures'2019: a short statistical compendium.) (In Russian)]. Petrozavodsk: Territorial department of the Federal State Statistics Service for the Republic of Karelia (Kareliaistat), p. 65.
24 Samujlova IN, Fedotova SYu., editors (2017). Nevrologiya. Standarty medicinskoj pomoshchi. [(Neurology: Health Care Standards.) (In Russian)]. Moscow: GEOTAR-media, ISBN: 9785970439265, p. 824.
25 Schmidt IE, Jahno NN (2016). Rasseyannyj skleroz [(Multiple sclerosis.) (In Russian)]. Moscow: Medpress, ISBN 978-5-00030-337-5, p. 272.
26 Sirenev IM., Gerasimova-Meigal LI, Sergeev AM, Ivanova GJu, Orlov PO (2019). Epidemiologiya rasseyannogo skleroza v Respublike Kareliya za period 2013-2018 [(Epidemiology of multiple sclerosis in the Republic of Karelia for the period 2013-2018.) (In Russian with English abstract.)] *Vest Ural Med Akad Nauk*. **16**(2): 315–319.
27 Strelnikova OV, Barabanova MA, Muzlaev GG (2014). Analiz epidemiologicheskoj situacii po rasseyannomu sklerozu v Krasnodarskom krae [(An analysis of the epidemiological situation on multiple sclerosis in the Krasnodar region (In Russian with English abstract.)] *Zh Nevrol Psikhiatr im S S Korsakova.* **114**(2 Pt 2): 20–24.
28 Vojinović S, Savić D, Lukić S, Savić L, Vojinović J (2015). Disease relapses in multiple sclerosis can be influenced by air pollution and climate seasonal conditions. *Vojnosanit Pregled.* **72**(1): 44–49. DOI: 10.2298/VSP140121030V
29 Waubant E, Lucas R, Mowry E, Graves J, Olsson, T., Alfredsson L et al. (2019). Environmental and genetic risk factors for MS: an integrated review. *Ann Clin Translat Neurol.* **6**(9): 1905–1922.
30 Zhelnin AV, Trushnikova TN (2008). Sravnitel'naya harakteristika i analiz rasprostranennosti rasseyannogo skleroza v Permskom krae, Sverdlovskoj, Tyumenskoj, Nizhegorodskoj oblastyah, CHuvashskoj respublike i Respublike Bashkortostan [(Comparative characteristics and analysis of disseminated sclerosis prevalence in Perm krai, Sverdlovsk, Tyumenn, Nizhniy Novgorod regions, Chuvash Republic and Republic of Bashkortostan.) (In Russian with English abstract.)] *Perm Med Zh.* **25**(5): 103–107.
31 Zikhova AR, Berezgova LM, Tlapshokova LB, Boyko AN (2013). Epidemiologicheskie harakteristiki rasseyannogo skleroza v Kabardino-balkarskoj Respublike [(Epidemiological characteristics of multiple sclerosis in the Kabardino-Balkarian Republic.) (In Russian with English abstract.)] *Zh Nevrol Psikhiatr im S S Korsakova.* **10**(Vyp. 2): 5–7.