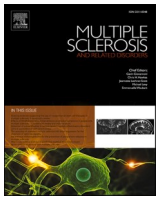
Multiple Sclerosis and Related Disorders 55 (2021) 103201

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard



Original article

Survey of diagnostic and treatment practices for multiple sclerosis in Russian Federation in comparison to European data

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ARTICLE INFO

Keywords:
Multiple sclerosis
Diagnosis
Treatment
Russian Federation

ABSTRACT

Introduction: The data of the survey of European (EU) neurologists on the methods of diagnosis and treatment of multiple sclerosis in Europe were compared with the data of the similar survey of neurologists of the Russian Federation (RF).

Method: Seventy-five neurologists specialized in MS from RF completed questionnaires on radiologically isolated syndrome (RIS), clinically isolated syndrome (CIS), relapsing-remitting (RRMS), secondary progressive (SPMS), and primary progressive (PPMS) multiple sclerosis.

Results: In the case of RIS, only 46% of neurologists from the RF recommended CSF analysis for oligoclonal IgG and only 54.3% performed magnetic resonance imaging (MRI) of the spinal cord, which is significantly lower than in the EU (78% and 80%, respectively).

In the case of CIS, significantly more neurologists from the Russian Federation would have tested for antibodies to disorders of the optical spectrum of neuromyelitis (57% in the EU and 94% in the RF). In case of typical RRMS, more neurologists from the RF preferred to start with the second line of disease-modifying therapy (DMT), a

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https://doi.org/10.1016/j.msard.2021.103201
Received 26 June 2021; Received in revised form 27 July 2021; Accepted 5 August 2021
Available online 8 August 2021

lower percentage would choose dimethyl fumarate as the first line DMT (9% in the RF and 25% in the EU). In case of escalating therapy, the majority of EU respondents (68%) indicated that one relapse would be sufficient (only 28% in RF), while in RF, 58% indicated that two relapses would be sufficient (22% in EU). Fewer neurologists from RF would use fingolimod, natalizumab or mitoxantrone for SPMS. 91% of neurologists in RF would like to prescribe ocrelizumab for PPMS.

Conclusion: MS specialists from RF are less active in monitoring RIS than MS specialists from EU. CIS is not indication to use any DMT in RF. MS specialists in RF are more conservative in changing DMT as escalation in cases with breakthrough RRMS. The products without indication to be used in SPMS are rarely prescribed in RF in comparison to EU. Most cases of PPMS in RF would be treated with ocrelizumab.

1. Introduction

In 2017–2018, surveys of MS specialists on optimizing the diagnosis and treatment of MS (EPEMS) were conducted in 11 countries of the European Union (EU). The survey involved 350 neurologists who completed a single questionnaire, and the results were published for the radiologically isolated syndrome (RIS), clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS) (Fernández et al., 2017) and later for secondary progressive MS (SPMS), and primary progressive MS (PPMS) (Fernández et al., 2018). The aim of this study was to compare data received from neurologists in the European Union (EU) and the Russian Federation (RF) in 2018–2020.

2. Methods

Full information about the methodology was provided in detail earlier (Fernández et al., 2017, 2018). A steering committee of MS neurologists from Europe used a modified Delphi process to develop case- and practice-based questions for survey distributed to MS neurologists. Survey 1 was composed of (i) questions about respondent demographics, (ii) questions about hypothetical patient cases, and (iii) questions related to diagnosis and overall management of MS. Survey 2 was composed of follow-up questions to provide additional detail for responses to questions from Survey 1 (Supplementary File 1). The results of both surveys are included and described separately. At first, the case-based questions were developed for the RIS, CIS, RRMS, and RRMS with breakthrough disease (highly active MS – HAMS) (Fernández et al., 2017), then later – for SPMS and PPMS, with pediatric MS and cases planning pregnancies (Fernández et al., 2018). The same questionnaire was translated into the Russian and validated (Boyko et al., 2020). The data resulted were compared with EU data using statistical methods ($\chi 2$ with Yates correction). Differences were considered statistically significant if $p < 0.05$.

3. Results

Seventy-five neurologists from different country regions took part in the survey in RF in 2019–2020. All responders participated in surveys (100%). Of these, 37% work in multidisciplinary hospitals, 20% – in clinics and university departments, 23% – in specialized MS centers (departments). 52% of respondents have more than 50 MS patients every month. More than 90% of responders have worked with MS patients for more than ten years, 54% – more than 20 years.

3.1. Radiologically isolated syndrome

The first case was a 31-year-old woman who underwent brain magnetic resonance imaging (MRI) to assess migraines. The MRI revealed white-matter pathology in the central nervous system corresponding to dissemination in space according to the MS diagnostic criteria (Fernández et al., 2017).

As a diagnostic study, only 46% of neurologists in RF recommended the analysis of CSF for oligoclonal IgG, only 54.3% performed MRI of the spinal cord (in EU – 80%), both significantly lower than in EU (78% and 80% respectively, $p < 0.05$). Neurologists in RF are less active in monitoring patients with RIS comparing with European. In cases with lesions in the spinal cord, 77% of neurologists from EU and only 54% of neurologists from RF ($p < 0.05$) will start disease-modifying therapy (DMT). The consensus in both groups of neurologists was not to prescribe DMTs (89% from RF and 96% from EU), 100% of Russian neurologists planned to conduct dynamic MRI control (in the EU – 94%), and 97% would repeat the MRI of the brain after six months, while in Europe – only 73% (no statistical difference). If lesions were found on a follow-up MRI, the decision to treat was dependent on the type, number, and location of lesions (**Table 1**). If new T2 lesions or Gd^+-lesions were detected, neurologists from RF seem to be slightly more active in diagnosing MS and prescribing DMT.

3.2. Clinically isolated syndrome

The second case was with CIS: a 24-year-old woman, previously healthy, has a loss of visual acuity in her right eye. Optic neuritis has been confirmed, and the results of a neurological examination are otherwise normal (Fernández et al., 2017).

There was general agreement that the following tests should be performed: brain MRI (100% both in EU and RF) and CSF analysis for oligoclonal IgG (84% in EU and 88% in RF). The majority of respondents would also perform a spinal cord MRI (74% in EU and 91% in RF), and visual evoked potential (70% in EU and 86% in RF) plus a serological examination (88% in EU and 94% in RF). At the same time, significantly more neurologists from RF would test for antibodies to neuromyelitis with optical spectrum disorders (NMOSD) (only 57% in EU and 94% in

Table 1
MRI lesions in the initial and follow-up MRI scans that would prompt DMT initiation in EU and in RF.

Lesions	RIS				CIS	
	Initial MRI		Follow-up			
	EU	RF	EU	RF	EU	RF
New or enlarging brain T2 lesions (RIS follow-up)	1 – 40% ≥1 – 51%	1 – 44% ≥1 – 61%	1 – 41% ≥1 – 61%	1 – 51% ≥1 – 77%	1 – 14% 2 – 34% ≥2 – 69%	1 – 15% 2 – 26% ≥2 – 63%
Brain Gd^+-lesions	≥1 – 29%	≥1 – 44%*	≥1 – 66%	≥1 – 94%*	1 – 78% 2 – 86% >2 – 91%	1 – 94% 2 – 100% >2 – 100%
≥1 new spinal cord lesion	30%	53%*	60%	83%*	86%	100%
MRI lesions would not prompt DMT initiation	T2 – 36% Gd^+ – 43%	41%	32%	41%	T2 – 17% Gd^+ – 10%	T2 – 10% Gd^+ – 5%

CIS, clinically isolated syndrome; DMT, disease-modifying therapies; EU, European Union; Gd^+, gadolinium-enhancing; MRI, magnetic resonance imaging; RIS, radiologically isolated syndrome; RF, Russian Federation.

* – difference with data from EU with $p < 0.05$.

RF, $p < 0.05$).

Respondents were almost unanimous (98% in EU and 100% in RF) about not treating with DMT this patient with a normal MRI and negative test of CSF for oligoclonal IgG. They also generally agreed (89% in EU and 96% in RF) that a follow-up MRI should be performed, with 75% in EU and 71% in RF performing the MRI within six months. Half of the respondents from the EU (46%) and only 26% from RF ($p < 0.05$) would consider initiating therapy if the patient had other less specific clinical symptoms (e.g. cognitive changes or fatigue).

If a brain MRI revealed demyelinating inflammation, most respondents would perform an LP (87% in EU and 97% in RF) and a spinal cord MRI (82% both in EU and in RF). There was strong agreement (Table 1) that the patient would be diagnosed with MS if the MRI revealed significant activity (e.g. a combination of Gd^+-lesion, 3 non-enhancing periventricular lesions). Neurologists from RF seem to be more active in early prescribing DMT in cases with active MRI.

The fundamental difference is in the opinion of specialists on the use of DMT in CIS patients. In the EU 100% prescribed DMT, while in RF CIS is not an indication for the use of therapy and none of the respondents would prescribe DMT until the diagnosis of MS.

3.3. Relapsing-remitting MS and breakthrough disease on therapy

The third clinical example is a typical RRMS in a 25-year-old patient (Fernández et al., 2017). In this case, 100% of neurologists from RF would conduct a course of DMT (in the EU – 82%). In cases with the first diagnosis of MS, the first-choice drugs in the proposed clinical situation differed significantly in EU and RF. The majority of responders in RF recommended a course of injectable DMT: 60% – glatiramer acetate (GA) or high-dose interferons-β – up to 50%, but more neurologists from RF preferred formally second-line DMT as the first choice (ocrelizumab, alemtuzumab, natalizumab) (Table 2). These new highly effective DMT dominated in responses from RF when the severity of the case was increased further (modification 1 and 2), significantly higher than in EU for anti-B-cells DMT and alemtuzumab for modification 2. A lower percent of neurologists from RF will choose dimethyl fumarate (DMF) as the first line drug (9% in RF and 25% in EU, $p < 0.05$) (Table 2).

MRI control within 6–12 months would be carried out by 100% in RF and 89% in EU. If there are no changes in the patient's condition for five years, then 94% in RF and 86% in EU would continue therapy.

In survey 1, respondents were asked to choose the minimum number of clinical relapses for both 6- and 12-month periods that would prompt them to suggest a change in DMT (Table 3). For a 6-month period, the majority of respondents from EU (68%) indicated that one relapse would suffice (only 28% in RF, $p < 0.05$), while in RF, 58% indicated that two relapses would suffice (22% in EU, $p < 0.05$). For a 12-month period, more neurologists from the EU would change therapy after one (36%) or two relapses (55%), while in RF only 12% and 50% correspondently ($p < 0.05$), up to 15% in RF – 3 relapses (in EU only 3%, $p < 0.05$) (Table 3). In the EU, the majority of respondents (51%) would suggest a change in DMT with one lesion (23% in RF, $p < 0.05$), whereas 32% indicated that two lesions would be necessary (37% in RF) and 17% said that more than two lesions would be necessary, and in RF 28% neurologists suggested to see ≥ three lesions.

Table 2
First treatment choice and treatments never chosen for patient case scenarios.

DMT	Initial case (%)		Modification 1 (%)		Modification 2 (%)	
	EU	RF	EU	RF	EU	RF
DMF	25	9*	12	17	10	12
IFN-β-1a IM	11	15	2	5	2	3
IFN-β-1a SC	14	31*	6	26*	5	8
IFN-β-1b SC	12	29*	5	23*	6	9
GA	9	60*	2	6	9	11
Teriflunomide	22	13	3	13	6	9
Ocrelizumab (anti-B-cell mAb)	1	9*	3	9	7	53*
Alemtuzumab	0	3	5	6	14	41*
Fingolimod	2	3	10	13	23	33
Natalizumab (JCV negative)	0	6	38	36	47	51
Natalizumab (JCV positive)	0	3	5	6	15	18
No treatment	3	6	0	3	NA	3

DMF, dimethyl fumarate; DMT, disease-modifying therapies; EU, European Union; GA, glatiramer acetate; IFN, interferon; IM, intramuscularly; JCV, JC virus; RF, Russian Federation; SC, subcutaneously; mAb, monoclonal antibodies.
* – difference with data from EU with $p < 0.05$.

Table 3
Minimum number of clinical relapses and MRI lesions that would prompt a suggestion to change DMT in RRMS patients.

RRMS activity	Percentage of patients					
	6 months		12 months		Any time	
	EU	RF	EU	RF	EU	RF
Number of clinical relapses						
1	68	28*	36	12*		
2	22	58*	55	50		
3	0	3	3	15*		
≥4	1	3	0	0		
Number of new or enlarging T2 lesions						
1-2					23	26
3-4					50	56
5-8					12	13
≥9					1	3
Number of Gd^+-lesions						
1					51	23*
2					32	37
≥3					17	28

DMT, disease-modifying therapies; EU, European Union; Gd^+, gadolinium-enhancing; MRI, magnetic resonance imaging; RF, Russian Federation.
* – difference with data from EU with $p < 0.05$.

3.4. Secondary progressive MS

The next case was a 48-year-old woman with MS has been on the same DMT for 14 years. She noticed the progressive loss of mobility regardless of clinical relapses over the past two years and received the diagnosis of SPMS (Fernández et al., 2018). Respondents from EU and RF were in general agreement (78% and 89% correspondingly) that the current treatment should be changed (Table 4).

The only products, which could be used for SPMS (with relapses) are IFN-β SC, ocrelizumab, and mitoxantrone. The most frequently selected new treatments in the EU were fingolimod (29%–34%) and natalizumab (25%–32%), while they, as well as DMF, do not have an indication to be used in SPMS. Significantly fewer neurologists from RF would use fingolimod, natalizumab, or mitoxantrone. The only one DMT selected at the same level for SPMS in EU and RF with the same frequency was monoclonal antibodies (mAb) to B-cells (ocrelizumab, ofatumumab and rituximab).

For those who would continue treatment, a majority (55% in EU and 52% in RF) indicated that other clinical evidence (e.g. cognitive changes or fatigue) would prompt them to switch to DMT.

3.5. Primary progressive MS

In the case of PPMS (Fernández et al., 2018), lumbar puncture and CSF analysis are mandatory everywhere (94% in RF and 97% in EU), with visual evoked potentials in the second place (86% in RF and 76% in EU). In the EU at that time, there was a general agreement (77%) not to initiate DMT. For comparison, 91% of neurologists in RF wanted to prescribe ocrelizumab for PPMS (94% in the presence of Gd^+-foci on MRI, 100% in the detection of oligoclonal IgG in the CSF). The dynamics of MRI are mandatory: a repeat within six months would be performed by 97% in the RF (88% in EU).

Table 4
Percentage of respondents who would switch SPMS patients progressing under treatment with each of four therapies to each of eight alternative therapies in the EU an RF.

Current therapy	New therapy Different type of IFN-β	GA	DMF	Fingolimod	Natalizumab	Anti-B-cell therapy	Teriflunomide	Mitoxantrone
IFN-β-1a IM RF (EU)	9	1	0	2*	5*	12	0	3*
	(10)	(2)	(8)	(29)	(27)	(11)	(2)	(11)
IFN-β-1a SC RF (EU)	3	0	0	6*	4*	11	0	3*
	(5)	(2)	(9)	(30)	(30)	(12)	(1)	(13)
IFN-β-1b SC RF (EU)	1	0	1	3*	3*	16	0	5*
	(4)	(3)	(9)	(30)	(32)	(11)	(1)	(12)
GA RF (EU)	7	0	0	2*	2*	15	3	2*
	(4)	(1)	(7)	(34)	(25)	(11)	(0)	(10)

DMF, dimethyl fumarate; EU, European Union; GA, glatiramer acetate; IFN, interferon; IM, intramuscularly; RF, Russian Federation; SC, subcutaneously; SPMS, secondary progressive multiple sclerosis.
* – difference with data from EU with $p < 0.05$.

4. Discussion

Neurologists from RF are less active in monitoring patients with RIS comparing with European ones. In cases with lesions in the spinal cord, 77% of neurologists from EU and only 54% of neurologists from RF ($p<0.05$) will start DMT therapy. This could potentially delay the time of MS diagnosis and the early start of DMT. However, if new T2-lesions or Gd^+-lesions were detected, neurologists from RF seem to be slightly more active in diagnosing MS and prescribing DMT.

Significantly more neurologists from RF would have tested for antibodies to neuromyelitis optical spectrum disorders (NMOSD) (57% in EU and 94% in RF, $p < 0.05$). This could be associated with the higher frequency of NMOSD in several populations (ethnic groups), especially in the Asian part of this large country. While no one has yet published data on the epidemiology of NMOSD in RF, the recent study in neighboring Kazakhstan with ethnically close population to Asian parts of Russia showed NMOSD prevalence up to 3.1 cases per 100000 population (Khaibullin et al., 2019), which is higher than in the majority of population of Europe (Hor et al., 2020).

Half of the respondents from the EU (46%) and only 26% from RF ($p < 0.05$) would consider initiating therapy if the patient with CIS had other, less specific, clinical symptoms (e.g. cognitive changes or fatigue). On the one hand, this demonstrated that neurologists from RF are not so attentive to less specific symptoms of MS or did not have an opportunity for testing cognitive function or fatigue in CIS. On the other hand, the regulatory / financial features may explain the more restrained attitude to the treatment of RIS and CIS because these indications are not included in RF for use of DMT.

At the same time, neurologists from RF seem to be more active in early prescribing DMT in cases with early diagnosis of MS and active MRI. 94% of responder from RF answered that the presence of Gd^+-lesions on MRI or ≥one new spinal cord lesion (83%) would prompt DMT initiation (66% and 60% correspondingly in EU).

In typical RRMS, more neurologists from RF preferred formally second-line DMT as the first choice (up to 9% for anti-B-cells therapy with ocrelizumab). This might at least in part reflect the higher frequency of diagnosis of highly active MS (HAMS) in the RF population when the second-line DMT is the first choice. Low percent of DMF in RF (9% and 25% in EU, $p < 0.05$) is associated with the fact that in RF the price of DMF is not covered by the state, only by local funds with lower opportunities.

In cases with escalating therapy in RRMS, the majority of respondents from EU (68%) indicated that one relapse would suffice (only 28% in RF, $p < 0.05$) for a 6-month period, while in RF, 58% indicated that two relapses would suffice (22% in EU, $p < 0.05$). EU neurologists are more active in changing DMT in cases with clinical relapses and the MRI changes, which would prompt such suggestion. EU neurologists are more active in changing DMT in cases with clinical relapses as well as for the MRI changes that would prompt a suggestion to change DMT. MS specialists from RF seem to be more conservative in changing DMTs and less active in changing DMT if inflammatory activity on MRI is present. Again, this could be explained by the regulatory/financial features, which may influence on higher thresholds for changing DMT in the breakthrough disease. The lists of patients who could receive new DMT (covered by the Federal State Program) are prepared once per 6 months. Patients indicating to change DMT (escalating) in many cases have to wait for at least six months to be included in the appropriate list. In this waiting period, the patient must receive a new DMT, covered by local foundations. However, it takes a lot of effort and additional documentation. In addition, the local funds' capacity is smaller than the state funds.

Significantly less neurologists in RF than in the EU would use fingolimod, natalizumab or mitoxantrone in case of SPMS. The first two do not have formal indications in SPMS, and regulators strongly control this in RF. The potential severe side effects of mitoxantrone decreased the frequency of its use in RF. The only one DMT selected at the same frequency for SPMS in EU and RF were mAb to B-cells (ocrelizumab, ofatumumab, rituximab).

In the EU at that time, there was a general agreement (77%) not to initiate DMT because there was no one DMT with indication to treat PPMS at that time period. The successful trial of ocrelizumab in PPMS (ORATORIO) published in 2017 (Montalban et al., 2017) open the window to use this DMT in PPMS and 91% of neurologists in RF wanted to prescribe ocrelizumab treatment for PPRS.

One of the main limitations of our study in comparison with the behavior of EU and RF neurologists in the diagnostic and treatment practices in MS is the different periods of the two surveys – 2017–2018 in EU and 2018–2020 in RF. This undoubtedly has affected the results, as the clinical practices have changed with the appearance of many new drugs, which have occurred in a very short time period. This reflects, for example, the difference in the attitude to use of DMT in PPMS, as the widely use of ocrelizumab in PPMS started in 2018.

Despite of these limitations, we believe that we have described the reality of the practice of diagnosing and treating MS in the RF compared to the EU, and this will allow us to make progress in reducing clinical variability, which would result in the improvement of patient's MS care.

5. Conclusion

In conclusion, it should be noted that in the EU, treatment with DMT begins earlier, already at the stage of CIS. However, this is primarily to be influenced by the different regulatory conditions of DMTs prescribing. In RF, where the tactics of patient management of MS could be slightly more active, the start with second-line DMT seems to be more often, while MS specialists in RF are more conservative in changing DMT. As for SPMS, DMT without formal indication to be used in SPMS is rarely used in RF compared to the EU, and 91% of neurologists from RF treat PPMS with ocrelizumab.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

All authors declare that there are no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2021.103201.

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