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CLINICAL AND EPIDEMIOLOGICAL FEATURES OF FAMILIAL MULTIPLE SCLEROSIS

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Objective: determination of the clinical and epidemiological features of familial multiple sclerosis (MS) in the population of Rostov-on-Don. *Material and Methods.* Subjects of the research were patients with idiopathic inflammatory demyelinating diseases (IIDD) numbering 806 people, among them 710 people with MS according to McDonald criteria (2010, 2017), living in Rostov-on-Don. *Results.* In the analyzed population 78 family cases were revealed; among them was a patient with clinically isolated syndrome (CIS), one with radiologically isolated syndrome (RIS) in 44 families. The general risk of repetition in the population demyelinating account for 3.7%. The prevalence rate of the familial MS in the population was 6.9 per 100000 people. In the male-to-female correlation for cases of familial MS makes 1:3.5. In most analyzed cases of familial MS (61.2%), a woman had the disease. The onset age in the first generation was considerably higher than the one in the following generations, on average 13.1±4.8 years more. The first remission continued 2.6 years in the familial MS group. In the group of the familial MS, the average disease development speed is 0.8±0.3 points per year. An analysis of clinical features revealed a predominance of polysymptomatic debut, which was noted in 20.63% of cases. *Conclusion.* A burdened family history in patients with MS may be an unfavorable prognostic factor for the aggressive course of the disease, and given the predominance of women as “progenitors”, it is possible to suggest the role of mitochondria in the pathogenesis of the disease.

Key words: multiple sclerosis, epidemiology, familial multiple sclerosis.

Introduction. Multiple sclerosis (MS), according to clinical surveys, is a chronic polyetiological autoimmune-mediated demyelinating disease. MS belongs to hereditary diseases. Its development is influenced by trigger factors (viral and bacterial infections, external environment factors, etc.) Though the contribution of each factor into disease development is not currently stated [1–5].

The research conducted using the twin method has shown that the other monozygotic twin has a 30% probability of MS emergence, whereas a heterozygotic twin has only 4%. The research also shows that monozygotic twins are more often discordant in the MS-susceptibility gene, despite being concordant in other hereditary diseases, which is an indirect proof that external causes are essential [6, 7].

Radiologic workup showed, that magnetic resonance imaging (MRI) of healthy monozygotic twin brothers or sisters of the patients with definite MS diagnosis, in 14% of cases shows focuses which are typical for MS [8]. Determining the risk factors, mainly modifiable, is necessary to estimate the importance of clinical surveys of MS, including familiar forms of MS.

The role of genetic predisposition to MS can be also observed through multiple studies revealing the fact that the risk of MS in the population is much lower than in the families that have a member with MS. The risk of MS emergence reaches 20% for three generations, which is 20–50 times more than for the population in general [8–11]. The analysis of the data of clinical features in the course of disease in the families didn’t show any prevailing significant features in the disease onset symptoms in generations; with every following generation, however, the age of onset diminishes and the disease progresses faster in every generation [10–13]. The large-scale studies in searching genes predicting MS have revealed more than 50 tentative alleles responsible for the following disease progress [14].

So, *the aim* of the research is to study the clinical and epidemiological characteristics of the familial forms of multiple sclerosis in the population of Rostov-on-Don.

Material and Methods. The research was done with the use of the data pools of the patients who undergo a

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Table 1

Clinical-demographic aspects of familial multiple sclerosis progression cases in comparison to the general group of patients with multiple sclerosis

Characteristics	Familial MS (n=78)	Sporadic MS (n=710)
Sex:		
Women	65 (78.8%)	472 (66.5%)
Men	14 (17.7%)	238 (33.5%)
MS onset age (years)	27.7±3.6	29.64±0.8*
Average point on EDSS	4.05±2.8	3.26±0.3*
Disease progression:		
RMS	48 (62.0%)	412 (58%)
Secondary progressive multiple sclerosis (SPMS)	30 (38.0%)	245 (34.5%)
Primary progressive multiple sclerosis (PPMS)	0	53 (7.5%)
Onset symptoms:		
Optic neuritis	11 (17.5%)	163 (23%)
Stem disorders	5 (7.9%)	78 (11%)
Sensation disorders	8 (12.7%)	85 (12%)
Pyramidal insufficiency	7 (11.1%)	107 (15%)
Cerebellar disorders	1 (1.6%)	50 (7%)
Pelvic disorders	0	21 (3%)
Polysymptomatic onset	13 (20.6%)	185 (3%)
Others	2 (3.2%)	21 (3%)
Unknown	31	0
Rate of progression (points per year)	0.8±0.3	0.1±0.05*

Note: * — p<0.05.

medical examination at the in-patient department or on an ambulatory basis of the Department of Nervous Diseases and Neurosurgery in Rostov State Medical University, in Multiple Sclerosis Medical Center; data from neurology departments and polyclinics, control date being 01.01.2018.

Subjects of the research were patients with idiopathic inflammatory demyelinating diseases (IIDD) numbering 806 people, among them 710 people with MS according to McDonald criteria (2010, 2017), living in Rostov-on-Don.

Disease severity was evaluated according to the level of neurologic impairment on the international scales: FS and the Expanded Disability Status Scale (EDSS), with the patients with recurring-remitting MS in remission. The following data were analyzed: age and onset symptoms, duration of the first remission, disease progression speed was evaluated as the dependence of the EDSS factor to the disease duration in years.

In the analyzed population 78 family cases were revealed; among them was a patient with clinically isolated syndrome (CIS), one with radiologically isolated syndrome (RIS) in 44 families (2 and more patients with RIS in the family).

Results. The general risk of repetition in the population (the percentage of relatives with MS inside the group of interest) is 3.7%. The family risk of repetition (the percentage of families of probands where there was another case of MS in the family) account for 5.0%. Family cases in groups of patients with idiopathic inflammatory demyelinating diseases account for 9.7%. The prevalence rate of the familial MS in the population was 6.9 per 100000 people.

In the male-to-female correlation for cases of familial MS, women prevail considerably and it makes 1:3.5 (male-to-female correlation in the group with sporadic MS was 1:2.2). In most analyzed cases of familial MS (61.2%), a woman (grandmother, mother or aunt) had the disease.

The onset age in the first generation was considerably higher than the one in the following generations, on average 13.1±4.8 years more. The first remission continued 2.6 years in the familial MS group.

Also, in the group of the familial MS, the average disease development speed is high: 0.8±0.3 points per year, though only 26.6% of patients had a soft type of relapsing multiple sclerosis (RMS) state with the progression speed less than 0.25 points per year.

When analyzing the clinical features of the onset symptoms, it was found that polysymptomatic onset prevails (20.6% of cases). In 15 families (34.0%) the disease was diagnosed for representatives of one generation (4 pairs of female twins). In 3 of them, every sister had MS, in the 4th pair one sister has MS, the other has RIS. In two pairs the disease originator was a woman (the twins' mother suffered from MS), which can also be a criterion for the role of mitochondria in carrying MS over. In 2 other families, 2 female siblings were observed, the younger one with MS, the elder one with CIS; note that the patient with MS had her disease onset at younger age, like in the other family, where two siblings have MS, and the brother's disease started at earlier age as well and progresses more aggressively. Clinical-de-

Table 2

Family Tree analysis of patients with multiple sclerosis

Family member with MS	N=78
Mother — daughter — daughter	2
Mother — daughter	7
Mother — daughter — granddaughter	1
Mother — son	4
Father — son	1
Father — daughter	6
Aunt — nephew	2
Aunt — 2 nieces	1
Uncle — niece	1
2 sisters	7
Brother — sister	5

mographic aspects of familial MS progression cases in comparison to the general group of patients with MS are presented in table 1.

First-degree family history was registered in 39 families, second degree — in 5 of them. In one family MS was diagnosed in 3 generations, in 31 families — in 2 generations, in 12 families — in 1 generation. Family Tree analysis of patients with MS are presented in table 2.

Discussion. Comparative analysis of the number of the MS family cases in the population revealed, that it has increased in comparison to the results of the studies held before [10–12].

The family cases in groups of patients with idiopathic inflammatory demyelinating diseases account for 9,7%, which is two times more than the measurement done in 2014 in the Tomsk region (4.7% of the general number of MS patients). The prevalence rate of the familial MS in the population was 6.9 per 100000 people; for comparison, in the Tomsk region, the prevalence rate was 1.4 cases per 100000 people [15].

The reason of the revealed prevalence of women of families of probands can probably be explained through the mutations originating in the mitochondrial DNA which is inherited by all the descendants without undergoing any changes. Many studies note the connection between inheriting a certain type of genes in a major histocompatibility complex and MS, and the presence of HLA DR15 phenotype was associated with younger onset age and female sex [16, 17].

The onset age in the first generation was considerably higher than the one in the following generations, this can be an indirect indicator that the disease is polygenic because the anticipation principle (accumulating the pathological genes in the following generations) is specific for them. The resulting data correlate to the results of some other research held earlier [15, 18]. At the same time, the other authors' data don't point at the firm connection of the familial forms of MS with the earlier onset age [16, 17]. When the first remission duration was analyzed in the familial MS group (2.6 years); maximum proximity to aggressive MS according to that indication was discovered (2.97±1.5) which can be an indirect indicator of a high risk of MS aggressive progress when there's one patient in the family.

Also in the group of the familial MS, the average disease development speed is high: 0.8±0.3 points per year, which is even higher than the aggressive type of MS (on average, in the group of relapsing-remitting MS it is 0.1±0.05 points per year, and of aggressive remitting MS it is 0.6±0.3, $p<0.05$), though only 26.6% of patients had a soft type of relapsing multiple sclerosis (RMS) state with the progression speed less than 0.25 points per year (in the group of sporadic MS 36.6% had soft type). The research done before show ambiguous results, the data in some of them correlate to the ones for our region; the other authors didn't reveal the firm connection between the familiar type of MS and the speed of disease development [15, 18].

When analyzing the clinical features of the onset symptoms, it was found that polysymptomatic onset prevails (20.6% of cases), which is also characteristic of the aggressive course of MS. In families where the disease is registered in representatives of one generation, in a patient with MS the disease debuted at an earlier age and proceeds more aggressively.

The genealogical analysis revealed the possibility of all the types of inheritance (autosomal dominant, recessive and sex-linked), which also supports the polygenetic nature of the disease.

Conclusion. Everything cited above leads us to the conclusion that compromised family medical history can be considered an unfavorable prognostic factor for MS progress.

In familial forms of MS, the amount of women outnumbers one of sporadic MS. Based on the prevalence of familial forms of MS, where the disease originator was a woman, it is possible to presume the role of mitochondria in the pathogenesis of the disease.

The genealogical analysis supports non-Mendelian inheritance, i. e. the possibility of all the types of inheritance. The phenotypic traits of familial MS are as follows: the disease onset in the following generations happens at an earlier age and increases the risk of aggressive progression, which allows us to consider the family history to be the risk factor for aggressive MS progression.

Conflict of interest. The authors declare that they have no conflict of interest.

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