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METHODS OF DIAGNOSIS AND TREATMENT

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COMPARATIVE ANALYSIS OF SPORADIC CASES AND FAMILY FORM OF PROGRESSIVE MUSCULAR ATROPHY OVER A 30-YEAR PERIOD (1986-2016) IN THE REPUBLIC SAKHA (YAKUTIA)

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ABSTRACT

Progressive muscle atrophy (PMA) is a rare disease of the motor neuron disease group (MND), which is characterized by selective lesions of the anterior horns of the spinal cord.

Objective: to study the features of the course of sporadic and family form of PMA over the period from 1986 to 2016.

Materials and methods: in 2006, a personalized register was introduced, which included patients with MND (amyotrophic lateral sclerosis, progressive muscular atrophy, progressive bulbar paralysis, primary lateral sclerosis). Since 1986 till 2006 patients were introduced after a retrospective study. The study included 15 patients with sporadic form and 5 patients from the same family. For the described study, patients with PMA were divided into 2 groups: 1 group included sporadic cases of progressive muscle atrophy (n=16), 2 group consisted of sick family members of a family case of 2 women and 2 men (n=4). Clinical examination of patients included assessment of somatic and neurological status in the onset of the disease and its further development, age of onset and duration of course.

Research methods: needle electromyography (EMG), Amyotrophic lateral Sclerosis Functional Rating Scale (ALSFRS) [9], spirography (LNG), forced vital capacity (FVC), magnetic resonance imaging (MRI), computed tomography (CT) of brain and spinal cord. In 9 cases, direct DNA diagnosis was carried out to exclude Kennedy's Bulbo-spinal amyotrophy.

Results: Our study revealed a moderate rate of progression in sporadic cases and a slow rate of progression in the family form of PMA. In our study, the duration of PMA was significantly higher in the family form and was 140±37.8 and 53.6±30.3 months in sporadic cases (p =0.003). In the family form of the disease, an earlier age of debut was observed than in sporadic PMA and in men the disease began earlier than in women.

Keywords: motor neuron disease, amyotrophic lateral sclerosis, progressive bulbar paralysis, progressive muscular atrophy, primary lateral sclerosis.

Introduction. Progressive muscle atrophy (PMA) is a rare disease from the group of motor neuron diseases (MND), which is characterized by selective damage to the cells of the anterior horns of the spinal cord and manifests itself by progressive muscle weakness, hypotrophy and fasciculations. On the recommendation of the World Federation of Neurologists, since 1994 severe neurodegenerative diseases with unknown etiology and unspecified pathogenesis, characterized by selective damage of central and/or peripheral motor neurons, were referred to motor neuron diseases. For diseases in MND group a typical progressive course with the same fatal outcome. This group includes amyotrophic lateral sclerosis (ALS), progressive muscular atrophy (PMA), primary lateral sclerosis (PLS) and progressive bulbar palsy (PBP) [12].

The most common in the world disease in this group is ALS, which accounts for 80% in this group. The share

of PMA is 9%, PBP-8% PLS-2% [6]. For the first time, 11 patients with progressive muscular atrophy described in 1850 F. Aran [1]. In 1874 J. M. Charcot cited differences in the clinical and pathological picture of amyotrophic lateral sclerosis and progressive muscle atrophy and isolated ALS and PMA into separate syndromes. Considering the El-Escorial criteria adopted by the world Federation of Neurologists in 1990 and processed in 1998, PMA is not synonymous with ALS and is a separate nosological form [12]. In 1880 W. Osler described progressive muscle atrophy in 13 patients in two generations of the Farr family in Vermont; new cases of the same disease were described later by M. Brown, V. CudKowicz and co-authors who first reported that the disease in the Farr family was caused by a mutation of the *A4V* gene encoding cytosolic protein, the copper-zinc-dependent superoxide dismutase (CuZn-SOD) enzyme [1]. The *A4V* mutation is identified in approximately half of ALS familial cases associated with mutations of CuZn-SOD in the North America. This mutation is characterized by malignant, rapidly progressive course, and the life expectancy of patients rarely exceeds 2 years, averaging 1.4 ± 0.9 years (n=84). In addition, in patients with *A4V* mutation, both clinically and pathomorphologically interest of only peripheral motor neurons was revealed. In Yakutia, the disease is rare. In the MND group the share of PMA is 13%.

Objective: to study the peculiarities of sporadic cases and family form of progressive muscular atrophy in the Republic of Sakha (Yakutia)

Materials and methods of the research. In the Health Institute M.K. Ammosov NEFU on the basis of the neurological department of the Republican hospital № 2 – Center for emergency medical care (RH №2-CEMC) from 01.01.2006 a personalized register of patients with motor neuron disease is performed, which includes all patients with MDN, regardless of the form of the disease. In this register, retrospectively since 1986, after studying the medical documentation, according to El-Escorial criteria, patients with clinically significant ALS were included, and from 01.01.2006 with probable and possible ALS. In addition, patients with progressive bulbar paralysis, progressive muscle atrophy and primary lateral sclerosis were included. All of them were observed in the neurological Department of the RH №2-the CEMC of Yakutsk. A total of 154 patients were included in the register as of 01.01.16, from which 124 were diagnosed with ALS (81%), 20 patients, including proband and sibs of the family case – PMA (13%), 4 patients - PBP (2.6%), 5 – PLS (3.3%).

For the described study, patients with PMA were divided into 2 groups: 1 group included sporadic cases of progressive muscle atrophy (n=16), 2 group consisted of sick family members of a family case of 2 women and 2 men (n=4).

Clinical examination of patients included assessment of somatic and neurological status in the onset of the disease and its further development, age of onset and duration of course. Needle electromyography was used to detect signs of damage to the PMN in acute and chronic denervation or denervation of the current-reinnervation process. Electrophysiological examination was carried out according to the Protocol of international recommendations for diagnosis of MND [10] to determine the rate of progression of the disease, the functional scale Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS) was used [9]. The functional deficit was assessed by a 4-point system. At the same time, the loss of 9-12 points for 12 months was regarded as a rapid rate of progression, from 5-8 points, as an average rate of progression, from 0-4 points, as a slow rate of progression. Spirography (LNG) was carried out both in newly admitted patients and in re-admission. LNG was used to determine the volume of forced vital capacity of the lungs (FVC) and to identify the degree of progression of respiratory failure (RF). Reduction of FVC to 70-80% and below and reduction of FVC by 15% in 3 months was noted as a rapid progression of RF [5]. In addition, standard clinical and biochemical blood and urine tests were performed. Patients included in the register since 2006 magnetic resonance imaging and computed tomography of the brain and spinal cord were performed to exclude diseases with similar clinical manifestations with MND. In 9 cases, after the patients filled in the informed consent, direct DNA diagnostics was carried out to exclude Kennedy's Bulbo-spinal amyotrophy. The family anamnesis and the compilation of the pedigrees were carried out in the course of the conversation with the patient and his relatives.

Results and discussion. In general, the group of PMA patients included in the personalized register was 20 patients, including 5 women and 15 men. In the first group with sporadic form of PMA (n=16) were 15 men and 1 woman. The second group consisted of 4 patients (n=4): a father and his children - 2 daughters and a son. Differential diagnostics was carried out as in sporadic cases and in a familial case: 1) hereditary Kennedy spinal-bulbar amyotrophy with X-linked recessive type of inheritance, which manifests itself in men in a relatively later age, usually after 40 years [8] and 2) genetically heterogeneous group of hereditary muscle diseases with similar phenotype of the disease - limb-girdle dystrophies (LGMD) 1A, LGMD 2A and LGMD 2N. For LGMD 1A typical dysarthria and dysphagia, may be present muscle weakness of the distal extremities; 2A LGMD, characterized by marked atrophy periscapular muscles, biceps, gluteal muscles, muscles of thighs; in LGMD 2N, possible late-onset and slower rate of progression [5]. The clinical picture in all the studied cases was typical for the phenotype of progressive muscular atrophy and was presented depending on the level of cerebrospinal axis lesions with flaccid paresis, amyotrophy, fasciculations, speech disorders, swallowing and phonation without sensitivity disorders, pelvic organ functions and cognitive impairment of Alzheimer's type. Needle EMG was performed in 15 cases (85%), in the remaining 5 cases EMG was not performed due to the severity of the patients. In all 15 cases, signs of anterior spinal cord injury were found. The absence of clinical symptoms of Central motor neuron lesion, as well as signs of neuronal denervation during needle EMG, as well as the absence of focal lesions on MRI and CT of the brain and spinal cord, characteristic of diseases with a similar clinical picture with ALS and PMA, allowed establishing the diagnosis of progressive muscle atrophy.

The age of onset of the disease in women with sporadic PMA was 57, 58 and 59 years, in men the average age was 54.2 ± 11.8 years. With familial form of the disease, the age of debut for women was 40 and 50 years, men 38 years father 32 years and have a son. By the average age of debut in both groups the differences in student's T - test are statistically insignificant (p =0.06). According to the Mann-Whitney test, statistically significant differences between the groups (p=0.003) were revealed in the duration of the disease: in sporadic cases, the duration of the disease was significantly shorter than in the family case. The average duration of the disease in the group with sporadic disease was 53.6±30.3 months, and in the group with the family form of the disease 140±37.8 months.

By the place of residence urban resi-

dents - 5, rural - 14. According to ethnicity, 12 people are of the Yakut nationality, 8 - Russian. In the study of clinical symptoms in women (n=3), in the group of sporadic PMA in one case the disease began with weakness in the left thigh with further development of a sluggish lower paraplegia. In the second case - with weakness in the right hand and the development of brachial paraparesis and gradual generalization of the process, in the third - with distal paresis of the left leg and subsequent development of hemi-and tetraparesis. In men (n=13) in the group of sporadic PMA the disease began in 10 cases with weakness in a hand, which is then passed into the brachial diplegia and flaccid tetraparesis. In the remaining 3 cases, the disease manifested itself as a lumbar debut. In men, the family PMA disease (n-2) began with weight loss of the hands, tremors in them, fasciculations of the muscles of the trunk with a gradual involvement in the pathological process of the lower extremities and bulbar disorders at the end of life. Both in the last 2 years of life were bedridden, suffered from severe swallowing and speech disorders. The father died at the age of 52 years. The son, who died at the age of 46 years, bulbar disorders joined only 10 years after the onset of signs of the disease. The course of the pathological process was slowly progredient and was 14 years in each case. The eldest of the two sisters had symptoms of the disease at the age of 40 in the form of weakness in the legs: she had difficulty in climbing the stairs and the bus. Gradually joined the weakness in the hands, there were atrophy of the hands, feet, fascicular twitching and bulbar disorders. During the last 2 years of her life she was bedridden, unable to move, roll over in bed, had difficulty eating due to swallowing disorders. She died at the age of 48. The disease duration was 8 years. Younger sister (born in 1950) lives permanently in one of the CIS republics and periodically comes to relatives in Yakutia. She became ill at the age of 50. The illness started as well as an older sister with weakness in the legs, began to move slowly, with difficulty to climb stairs, could not hold the spoon, cup and other items. Atrophy of hands and feet, blurred speech appeared. Currently, the clinical picture of the disease in this patient is manifested by sluggish deep proximal tetraparesis, distal tetraplegia and moderate bulbar disorders, without pelvic and sensitive disorders. She moves in a wheelchair with assistance. The duration of her disease is currently 14 years. All members of the described family belong to the Yakut ethnic group [2].

The cause of all deaths (n=18) is respiratory failure. 1 patient with a sporadic form of PMA was connected to the ventilator for 12 months. The duration of the disease was 38 months in this patient. According to the ALSFRS scale, the rate of progression in the family case was attributed to the slow type and amounted to the loss of functional activity from 2 - 4 points per year. In sporadic cases, the loss of functional activity was higher and amounted to 5-8 points per year, and the rate of progression was attributed to the average rate.

Conclusions. As a result of clinical observation, isolated lesion of peripheral motor neuron at different levels of the spinal cord was revealed in all 20 cases of MND. In this case, signs of involvement in the pathological process of the central motor neuron were not observed throughout the duration of the disease. Bulbar and respiratory disorders joined gradually as progression. The lethal outcome came from respiratory failure, due to aspiration pneumonia, paresis of the diaphragm muscles and auxiliary muscles involved in the act of breathing.

In general, the described cases of PMA are characterized by a moderate rate of progression in sporadic cases and a slow rate of progression in the family form of the disease. The obtained data correlate with the data of researchers from the United States [9], who compared the survival rate of patients with PMA and LAS on the example of 962 patients, of which 91 were with PMA and 871 with LAS. In the study, the survival rate of patients with PMA was significantly higher than that of patients with LAS. In our study, the duration of PMA was significantly higher in the family form and was 140±37.8 months against 53.6±30.3 months in sporadic cases of PMA (p=0.003). Although at the familial form of the disease earlier age of debut was observed.

In the described family case of PMA, an autosomal dominant type of inheritance from a sick father was established for three of six children: proband and his two older sisters [3, 4]. In the clinical picture of the disease, attention is drawn to the relatively early debut of the disease in males 32 and 38 years and the onset of the disease from the distal upper extremities, while in women, the disease began later: in 40 and 50 years with weakness in the proximal lower extremities. In all cases, there is a slow progression of the disease.

Thus, both sporadic and hereditary forms of PMA were registered in Yakutia, which are characterized by clinical polymorphism. Reported cases of PMA need further in-depth study using molecular-genetic and high-tech research methods. The results could help to reveal the immediate and probable causes of the etiology and pathogenesis of not only progressive muscle atrophy, but also other diseases of the group of motor neuron diseases.

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PHARMACOLOGICAL AND SURGICAL TERMINATION OF MISSED ABORTION IN THE FIRST TRIMESTER AT THE DEPARTMENT OF GYNECOLOGY №1 OF THE SBI RS (YA) YAKUTSK CITY CLINICAL HOSPITAL

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ABSTRACT

This article demonstrates the advantages of pharmacological medical termination of missed abortion. It presents an analysis of women's experiences of pharmacological and surgical terminal of missed abortion based on material from the Department of Gynecology №1of the SBI RS (Ya) "Yakutsk City Clinical Hospital (YCCH)". The study included only patients with normal hemostatic system parameters. Patients with MA who have contraindications to the use of Mifepristone and Misoprostol were also not included in the group. The comparison group included 69 patients with MA, who underwent a surgical method of emptying the uterine cavity by vacuum aspiration. All patients were under observation in the gynecological department of the YCCH. To establish the diagnosis of MA a female pelvic ultrasound scan was performed using a vaginal sensor. The ultrasound control diagnosis was performed on the 14th day after taking Misoprostol and the vacuum aspiration.

The complications and treatment options are presented.

Keywords: embryo, anembryonic gestation, missed abortion, endometritis, pharmacological termination of missed abortion, vacuum aspiration, mifepristone, misoprostol, removal of embryo or fetus, hematometra.

Introduction. A missed abortion (MA), also known as a missed miscarriage or a silent miscarriage, is a pathology, in which for some reason the embryo (or fetus) ceases to develop and dies. The missed miscarriage takes a dominant position in the prevalence of reproductive losses.The incidence of MA is about 16-18% among pregnant women, and in the non-carrying prevalence of pregnancy, it reaches 45-88.6% of the number of spontaneous miscarriages at early stages. Endocrine dysfunctions, chromosomal abnormalities, different sexually transmitted infections, an insufficient amount of progesterone or an excess of androgens may lead to this pathology. Antiphospholipid syndrome can often be the cause of embryonic death when clots form inside blood vessels. Moreover, the reasons for embryonic death could be toxic effects from radiation, alcohol and illegal drugs consumption, smoking. The International Federation of Gynecology and Obstetrics adopted a scientific concensus, according to which each case of MA is associated with chronic endometritis (XVIII FIGO Congress of Gynecology and Obstetrics: Kuala Lumpur, Malaysia, 2006). In chronic endometritis an endometrial lesion is accompanied by the development of receptor deficiency, the sensitivity of the mucous membrane of the uterus (endometrium) to steroids decreases, and the deficiency of cyclic transformations of the endometrium is marked. This may lead to the disruption of implantation processes and, as a consequence, to MA.

In most cases the interruption of MA occurs independently, without any intervention in the uterine cavity, which reduces the risk of surgical, anesthetic, infectious inflammatory complications and reduces the psychogenic trauma for the patient [5]. Frequently, however, there is fetal egg retention and the question emerges about the most moderate way of eliminating it from the uterus. It has now been proven that the surgical method of emptying the uterine cavity during the MA is dangerous, since it facilitates to additional traumatization of the endometrium, which can complicate the achievement and the course of a subse-