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# THE FAMILY CASE OF OCULOPHARYNGEAL MYODYSTROPHY IN UST-ALDANSKY DISTRICT OF THE REPUBLIC SAKHA (YAKUTIA)

**Abstract:** This study was carried out to study the clinical and genetic characteristics of a family with oculopharyngeal muscular dystrophy in the Ust-Aldan district and to draw up a plan for the introduction of such patients. As a result, it was revealed that in two patients (proband and sibs) examined earlier, there was a progression of symptoms in the form of an increase in muscle weakness and movement disorders. Given the course of the disease, characterized by the steady development of symptoms of the disease, which leads to a decrease in the quality of life, patients with OPMD need to undergo symptomatic therapy courses in a specialized neurological department, inform the population about the pathways of disease transmission, about prenatal diagnosis and adequate available interventions and supportive care to reduce risk of suffocation and other complications of OPMD.

**Key words:** oculopharyngeal myodystrophy, autosomal dominant inheritance, *PABPN1* gene, family case, eyelid ptosis, progressive muscle weakness, hypotrophy of the proximal extremities, dysphagia, dysphonia, Yakuts.

**Introduction.** The staff of the YSC CMP together with the Research Institute of Medical Genetics (Tomsk) have been conducting research on a number of hereditary diseases of the nervous system for several years. Based on the analysis of the results of genetic and epidemiological studies, several hereditary diseases were identified that have a high prevalence in the Yakuts in comparison with the world population: type 1 spinocerebellar ataxia (46 cases per 100,000), myotonic dystrophy (21.3 cases per 100,000), hereditary enzymopenic methemoglobinemia (14.9 cases per 100,000), oculopharyngeal muscular dystrophy (12.6 cases per 100,000), Kennedy spinal bulbar amyotrophy (15.3 cases per 100,000), Friedreich's ataxia (2.8 cases per 100,000 ), 3M syndrome (12.7 cases per 100,000) [2].

Oculopharyngeal muscular dystrophy (OMIM 164300) is a rare progressive, hereditary, disabling disease of the neuromuscular system. The highest frequency of OPMD is found in populations with the "founder effect", such as Bukharian Jews - 1: 600 people. (Israel) [8] and the French-Canadian population (Quebec, Canada) - 1: 1000 people. [12]. In Europe, the incidence of this disease is 1: 100,000 [12], in the Republic of Sakha (Yakutia) it is 12.5 per 100,000 people and occurs mainly among the indigenous Yakut population. To date, more than 47 families (60 patients) from all over the republic have been registered, the largest number of families (11 families, 15 patients) with OPMD is observed in the Ust-Aldan district [4], where this disease is most common along with type 1 spinocerebellar ataxia (SCA 1, the prevalence is 46 cases per 100,000 population [7]). The cause of the disease is a mutation - expansion of trinucleotide GCN repeats in the *PABPN1* gene.

The disease is late manifesting, the onset of the disease is manifested in 40-60 years. An accurate diagnosis can only be made by a molecular genetic research method. Molecular genetic diagnosis of OPMD (mutation identification (GCN) 14) was introduced into the medical genetic consultation in Yakutia in 2008 [1].

In the clinical picture, progressive hypotrophy and muscle weakness in the proximal extremities, bilateral ptosis of the eyelids, hoarseness and dysphagia are observed. Death usually occurs from respiratory failure, due to impaired swallowing, leading to aspiration pneumonia, pulmonary infections and asphyxia [9].

Oculopharyngeal muscular dystrophy has an autosomal dominant mode of inheritance, but cases with a recessive mode of inheritance have been described [6, 10].

The age of onset of eyelid ptosis in patients with OPMD is on average 48 years (26-65 years), dysphagia is 50 years (40-63 years). Other symptoms are observed in patients as the disease progresses. Atrophy and weakness of the tongue (82%), atrophy and weakness of the proximal lower extremities (71%), dysphonia (67%), ophthalmoplegia (61%), weakness of the facial muscles (43%) and atrophy and weakness of the proximal upper extremities (38 %). At the same time, it was found that the earlier bilateral ptosis of the eyelids and dysphagia appeared in patients with OPMD (up to 45 years old), the earlier muscle weakness developed in the proximal regions (up to 60 years old), which led to a more severe course of the disease. The cases of severe course of the disease were 5-10%. [11, 12]. - raise from the results above to the introduction.

The aim of the study was to study the clinical and genetic characteristics of a family with oculopharyngeal muscular dystrophy in the Ust-Aldan district and draw up a plan for the introduction of such patients.

**Materials and research methods.** The material was collected during an expedition trip to the Ust-Aldansky district of the RS (Y), v. Borogontsy, v. Syrdaakh and v. Arylaakh under a bilateral agreement between the YSC CMP and the administration of these villages to examine the population in order to identify new cases of OPMD and other hereditary diseases. Were collected 102 samples of biological material (blood), of which 14 were taken from family members with a burden of heredity according to OPMD. Samples of biological material were placed in the collection of biomaterial at the YSC CMP.

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Research methods.

1. Genealogical method. The pedigree of a family from the Ust-Aldan district was studied. The pedigree (Fig.) included 5 generations, a total of 64 people in the pedigree fragment. I, II generation - deceased parents, III generation - patients and their siblings, IV - children of the proband and siblings of the proband, V - children who have not reached the age of onset of the disease. In the I-IV generations there are patients with OPMD, a total of 8. Presymptomatic carriers of the mutation out of those studied in the IV-V generations - 4 people.

2. Molecular genetic method.

All participants in the study underwent DNA diagnostics of the subject carriage of the mutation in the *PABPN1* gene. Molecular genetic research was carried out in the laboratory of hereditary pathology of the OMG YSC CMP. DNA was isolated from 10 ml of peripheral blood by the standard method using proteinase K followed by phenol-chloroform extraction (Medical laboratory technologies, 1999). Previously, written informed consent was obtained from all subjects for molecular research.

3. The clinical research method included an assessment of the somatic and neurological status. Two patients with OPMD (proband and sibs) were examined and examined by the molecular genetic method in 2008 and were examined again during an expedition trip in 2018.

**Results and discussion.** Of the 14 patients of the burdened family (n = 14), 7 (n = 7) had two alleles: normal - 6th and pathological allele - 10th. For the first time, a mutation in the PABPN1 gene — an expansion of the GCN repeat in the PABPN1 gene — was found in 5 patients from the same family (the genealogical scheme is shown in Fig.). The remaining 7 patients were found to have two normal alleles - 6/6. Thus, out of 14 members of one family, 7 carriers of the mutant gene were found with the development of a clinical picture of the disease after 60 years in 2 family members. The rest of the family members are in the preclinical stage of the disease.

Were examined 14 members from 1 burdened family (Fig.). At the same time, in two patients (proband and sibs), examined earlier, there was a progression of symptoms in the form of an increase in muscle weakness and movement disorders. In the clinical picture of the disease in both patients, drooping of both eyelids (eyelid ptosis), difficulty in swallowing liquid and solid food, nasal voice and hypotrophy (weakness) of the shoulder and thigh muscles are observed.

Proband N., (III-5, fig.) 1945 y. First examined at the age of 62. In the clinical picture of the disease: bilateral ptosis, dysphagia, external ophthalmoplegia, dysarthria, weakness of the facial muscles, hypotrophy of the shoulder, sub- and supraclavicular, subscapularis, gluteal muscles. At the age of 72, complaints: difficulty in walking, inability to cross a small threshold, to get up from a sitting position on their own. He considers himself ill from the age of 46, when rapid fatigability appeared and the upper eyelids began to drop. After 50 years, choking and nasal symptoms appeared. In the neurological status: a patient of high stature, asthenic constitution. Distinguishes odors. Visual acuity is reduced due to presbyopia. Pupils D = S, rounded. Already the left palpebral fissure, the eyelids close the upper third of the pupil (operated on for ptosis in 2008). The photoreaction is reduced. External ophthalmoplegia. No nystagmus. Trigeminal points are painless on palpation. The chewing muscles are affected. Sunken temporal fossa. The nasolabial fold on the right is less pronounced. Puffs out her cheeks and bares her teeth weakly. Hearing acuity is reduced on both sides, there is a hearing aid on the right. The pharyngeal reflex is reduced, the perception of taste is not impaired. Snuffiness, dysphagia. The soft palate is inactive during phonation. Raises shoulders and turns head satisfactorily. Tongue - deviation to the right, without fibrillation and atrophy. Marinescu-Radovic's symptom D = S ++.

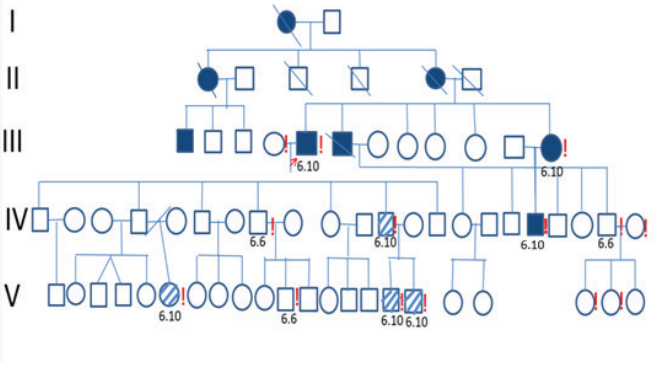


**Fig.** Fragment of the pedigree of a family with OPMD with the results of DNA analysis for a mutation in the PABPN1 gene;
Note. 6/6; 6/10 - results of DNA analysis for mutation in the PABPN1 gene ;! - personally examined patients; filled square - patient with OPMD, empty square - clinically healthy; the shaded square is a clinically healthy carrier of the mutation in the PABPN1 gene. I, II generation - deceased parents, III generation - patients and their siblings, IV - children of the proband and siblings of the proband, V - children who have not reached the age of onset of the disease.

He cannot raise his arms and legs, bend his legs at the knee joints, does not stand up independently from lying and sitting positions. Hand strength D = 13kg, S = 19kg. In the proximal parts of the arms, the strength was reduced to 3 points, in the distal parts to 4 points, in the proximal parts of the legs to 2 points. Muscle tone is diffusely reduced. Wide interscapular space. Hypotrophy of the subscapularis and subclavian muscles, more on the right, hypotrophy of the biceps and triceps muscles, Weakness of the iliopsoas on both sides. Hypotrophy of the gluteal muscles, quadriceps muscles. Deep tendon reflexes from the arms and legs are reduced, no difference in sides. There are no pathological signs. Coordination tests, PNP performs satisfactorily, CPR cannot raise his legs. Stands in the Romberg position. Duck gait. Superficial and deep sensitivity are not disturbed.

Sibs probanda T. (III-12, fig. 1), born in 1943 for the first time independently applied to a medical genetic consultation at the age of 64. Considers himself a patient since 51 years old, when complaints of general weakness, periodic coughing when swallowing, nasal voice, drooping of the upper eyelids appeared within 2 years. In the clinic in 2008: ptosis, external ophthalmoplegia, dysphagia, nasal tone, poorly intelligible speech, weakness of facial muscles, weakness of the subscapularis muscles and lower extremities. Objectively at the moment: general condition of moderate severity, general emaciation is expressed, asthenic. Neurological status: hypomimia, dysphonia. Low standing of the eyelids, almost complete ptosis on both sides. Pupils S> D, photoreaction is reduced, paresis of abduction in both directions, paresis of gaze upward. Diplegia n. facialis. The soft palate is motionless during phonation. The pharyngeal and palatal reflexes are absent. There are no atrophies and fasciculations. Severe atrophy of all muscle groups of the trunk and limbs. Tendon reflexes are absent from the hands, knee and Achilles are reduced. Tetraparesis is predominantly proximal. Does not move independently. No sensitivity disorders. He does not perform coordination tests due to weakness in the limbs.

Neurological examination in the dynamics of the proband and siblings of the

N. family showed that both patients had a pronounced progression of the disease in the form of an increase in bilateral ptosis, impaired swallowing, and the development of flaccid tetraparesis. At the same time, the proband could hardly move, and the sibs had a pronounced deep tetraparesis, as a result of which the patient could not move independently. Both patients required palliative therapy and nasogastric tube placement. The rest of the family members examined during the expedition had no symptoms of OPMD. In the clinical picture of the disease, as the symptoms progress, the greatest danger is dysphagia, which leads to aspiration of food into the respiratory tract and, as a consequence, to the development of aspiration pneumonia. Palliative neurology in OPMD involves tube feeding or stoma placement. There is currently no effective treatment. Techniques have been described to dissect the cricopharyngeal muscle to improve swallowing but not prevent aspiration. If ptosis interferes with vision, use special adhesive tape on the eyelids, wire eyelid holders, which are attached to the frame of glasses, or, if there is no pronounced weakness of the facial muscles, they resort to surgical treatment [3, 5]. From the anamnesis of patients and their medical records, it was established that patients received once a year symptomatic drug treatment at the place of residence. The drugs were prescribed for oral administration, in view of movement disorders, such as Carniel 2.0 mg 2 times - for a long time, Cytoflavin, milgamma, Dibazol 5 mg 3 times a day, Neuromidin. Such a course of treatment is insufficient for the restorative treatment of such patients, let alone palliative therapy. Patients do not have the opportunity to receive massage, physiotherapy exercises, physiotherapy electrical procedures. Although adequately prescribed therapy cannot cure the patient, it can improve his quality of life and prolong his life.

**Conclusion.** Taking into account the course of the disease, characterized by the steady development of the symptoms of the disease, which leads to a decrease in the quality of life, patients with OPMD need to undergo courses of symptomatic therapy 2 times a year in a specialized neurological department. Physicians should advise patients on what to expect as OPMD progresses, and discuss available interventions and supportive care to reduce the risk of choking and other complications of OPMD.

Such counseling can reduce the emotional burden of the disease. Patients with burdened families of OPMD, medical workers responsible for managing patients, as well as all people with rare diseases, need reliable, up-to-date information about the disease. For a timely diagnosis, it is necessary to conduct health education among the population and among families with a burdened heredity of OPMD, observing all the rules of bioethics. Early diagnosis in burdened families will allow prenatal diagnostics to reduce the burden of the disease in the population, as well as presymptomatic treatment in case of carriage of the pathological PABPN1 gene. The difficulty of making a diagnosis is associated with the late onset of the disease (40-60 years), especially in families with an undetected burdened heredity. Therefore, public health education plays an important role in timely diagnosis. In addition, timely diagnosis will provide an opportunity for early career guidance of the patient. Develop useful habits of a healthy lifestyle, limit hard physical labor, while receiving all symptomatic therapy, such as correction of ptosis of the eyelids using blephoroplasty and cricopharyngeal myotomy, will improve dysphagia in the early stages of the disease, as well as chemodenervation with botulinum toxin A into the cricopharyngeal muscle. In the later stages, surgical methods of treatment will not be effective. It is necessary to continue cooperation with the Ust-Aldan district for further work on health education of the population.

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