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DENTATORUBRAL-PALLIDOLUYSIAN ATROPHY IN THE SELECTION OF UNIDENTIFIED SPINOCEREBELLAR ATAXIES IN YAKUTIA

ABSTRACT

A clinical genealogical and molecular genetic analysis for the presence of mutations in the *DRPLA* gene in patients with an unidentified form of cerebellar syndrome in Yakutia was carried out.

Expansion of CAG repeats in the *DRPLA* gene was found in four members of the Yakut family. Clinical symptoms of patients with dentatorubral-pallidoluysian atrophy (DRPLA), a rare form of autosomal dominant spinocerebellar ataxia, from the Yakut family – ataxia, extrapyramidal and psychiatric disorders – it can be attributed to a later debut with a small degree of expansion of CAG repeats.

Keywords: dentatorubral-pallidoluysian atrophy (DRPLA), expansion of trinucleotide repeats, autosomal dominant disease.

INTRODUCTION

Dentatorubral-pallidoluysian atrophy (MIM 125370) is an autosomal dominant neurodegenerative disease characterized by the variability of combinations of progressive ataxia, epilepsy, myoclonus, choreoathetosis and dementia. The disease can begin at the age of 1 to 6 years of life. The cause of the disease is the expansion of CAG - repeats in the gene of *DRPLA* localized on chromosome 12p13 coding protein with an unidentified function (atrophin) [3]. Normally, the number of tandem CAG repeats is ≤36, and for pathologies from 40 to 100 [1, 2].

An important diagnostic sign of DRPLA is the detection of cerebrum in MR tomograms, in addition to nonspecific atrophic changes in the cerebellum, brainstem and the cerebral hemispheres, foci of demyelination in the white matter of the periventricular region, and the seminal center of the cerebral hemispheres [1]. In families burdened with DRPA, there is often an anticipation and the phenomenon of "father's transfer." The duration of the disease usually does not exceed 15 years. Morphologically, DRPLA is characterized by degenerative changes in the jagged nucleus, the outer segment of the pale ball and their projection zones in the red and lyus cores, and atrophy of the cortex of the cerebral hemispheres [4].

Analysis of clinical-genetic correlations showed that the different degree of expansion (CAG) -repeat of the gene of DRPLA leads to the manifestation of two phenotypes of the disease, different in clinical syndrome and severity. With a small degree of expansion (CAG) repeats of the *DRPLA* gene, a later debut and the development of choreoathetosis, ataxia, and mental disorders ("pseudo chorea") are observed, while in patients with the maximum repeat length of the *DRPLA* gene, the disease manifests itself at an earlier age with a severe syndrome of progressive myoclonus-epilepsy and dementia [5, 8].

Currently, DRPLA is considered an ethnic disease of the Japanese, the prevalence ranges from 0.2 to 0.7 per 100 000 [8], while in Europe and America only single cases are described [3, 4, 7, 8]. According to the Republican genetic register, in Yakutia, there are 519 patients with cerebellar syndrome, 80% of them are the autosomal dominant spinocerebellar ataxia (AD SCA) of the 1st type, with 20% of the forms remaining unidentified [2]. As is known, the Republic of Sakha (Yakutia) is a cluster of accumulation of SCA1, its prevalence rate for SCA1 has doubled over the past 21 years, reaching 46 cases per 100 000 population [6]. Given the prevalence of DRPLA in East Asia (Japan), it seems relevant to study this form of cerebellar ataxia in Siberian populations where unidentified forms of blood pressure of the AD SCA are recorded.

The aim of the work is a clinical genealogical and molecular genetic analysis for the presence of mutations in the *DRPLA* gene in patients with an unidentified form of cerebellar syndrome in Yakutia.

Materials and methods of research

In the period from 2008 to 2012, samples of biological material were sent to the Laboratory of Hereditary Pathology of the Department of the Molecular Genetics Yakut Scientific Center CMP, 80 patients, including 66 with sporadic form of SCA and 7 family cases with SCA (2 patients) were sent to genetics. Molecular-genetic part of the research was carried out jointly with colleagues from the Research Institute of the brain of the University of Niigata (Japan). On the basis of the department of molecular genetics of the YSC CMP, the work continued on the genetic analyzer Applied Biosystems 3130. The results of the sequencing were processed using the GeneMapper software.

DNA was isolated from 10 ml of peripheral blood by a standard method using proteinase K and subsequent phenol-chloroform extraction (Medical Laboratory Technologies, 1999). Previously, all informed subjects received written informed consent.

Results and discussion

Differential diagnosis of 80 patients with an unidentified form of cerebellar syndrome was performed on five forms of blood pressure in the SCA. Expansion of CAG repeats in the *ATXN2* (SCA2), *ATXN3* (SCA3), *CACNL1A4* (SCA6), *TBP* (SCA17) genes was not detected in the sample. The expansion of CAG repeat in the *DRPLA* gene (DRPLA) in four patients from one Yakut family was detected (Fig. 1). The proband and the brother have 63 mutant CAG repeats, the mother and sister of the proband have 62 (normal repeat ≤ 36).

III-5 proband R., born in 1969, first applied to the Medical Genetic Consultation in 2005 with a violation of coordination. In status: a patient of high stature, asthenic physique. Pupils D = S, photoreaction alive, left eye faint a little narrower. The volume of movement of the eyeballs is slightly limited in sides, horizontal bilateral nystagmus. The face is symmetrical. The soft palate is mobile, symmetrical. Swallowing is not broken. A voice with a nasal hue. The tongue is on the middle line, without fibrillation and atrophy. Light symptoms of oral automatism. There is no sharp paresis of

the extremities. Muscle tone is diffusely reduced. Hand dynamometry: D = 29 kg, S = 30 kg. Deep tendon reflexes from the hands and feet are slightly reduced, with no difference in sides. There are no pathological signs. The sample coordinator performs with intent and ataxia from both sides. Easy dysmetry and adiadochokinesia. In the Romberg position it is difficult, ataxia of the trunk. Gait is ataxic. Scale for the assessment and raiting of ataxia (SARA) was 25 points. Surface and deep sensitivity are not violated. MRI of the brain of 13.10.2010.

Conclusion: MRI-signs of cerebral atrophy, with the predominant lesion of stem structures and the cerebellum. EEG on February 20, 2012. Conclusion: Unexpressed diffuse changes. Moderate dysfunction of subcortical-stem structures. During the entire recording, rare bursts of epiactive ("acute-slow wave") are recorded along the anterior parts of the brain for up to 1 second.

II-1 mother of proband K., born in 1945, first applied to the Medical Genetic Consultation in 2006 with complaints about gait violation. She considers herself to be a patient from the age of 50, since 2001 she has had a speech disorder, and occasionally she has turned a blind eye. The pedigree is unknown, was brought up in the orphanage. In the status: in consciousness, the situation is compulsory, the facial features are pointed. The pupils are rounded, equal, and the photoreaction is weakened. The volume of orbit movement is limited when looking up, nystagmus is not present. Nasolabial folds are symmetrical, deep. The soft palate is symmetrical and mobile. Swallowing is not broken. The voice is nasal. Language - easy deviation to the right, without atrophy and fibrillation. Moderate proboscis reflex, symptom Marinescu - Rodovici on both sides. Speech is a rough dysarthria. The patient cannot stand and sit down unassisted, sits with support. In rest there is a tremor of the head and trunk, violent movements of the lower jaw, lips. Muscle tone is diffusely reduced. Hand dynamometry: D = 10 kg, S = 9 kg. Hypotrophy of hypotenor brushes. In the legs, strength is reduced to 3.5 b. Contracture of the right knee joint. Tendon reflexes from the hands: carporadial living, D = S, with biceps and triceps slightly reduced. Knee and Achilles reflexes are low, S> D. There are no pathological signs. Patient K. performs finger-to-nose test with intention, mild choreoathetosis. Scale for the assessment and raiting of ataxia (SARA) was 33 points. Hyperesthesia of the extremities. Deep sensitivity is slightly broken. There are no pelvic disorders. She is confused in date and in the names of grandchildren. It is worth noting that in the mother of proband cerebellar syndrome is combined with extrapyramidal insufficiency and dementia. These clinical symptoms coincide with the literature data on DRPLA.

III-3 sibs of proband, N., born in 1966, female, first applied in December 2010 with complaints of gait disturbance, speech changes, handwriting, sharp vision loss, coordination disorder, forgetfulness. After 40 years the husband of the patient noticed a violation of her gait, and then joined the change of speech and forgetfulness. Her surrounding begins to make comments that she forgets specially. Since the beginning of 2011, she has noticed outbursts of anger. Since 2010, there are attacks of severe headache in the frontal region with a feeling of nausea and vomiting, connects to stressful situations, a frequency of 1 time in 2-3 months, at this time does not accept anything, does not seek medical help, while there is a decrease Blood pressure to 60/40 mm Hg. Art. Within two years does not work, has the 2nd group of disability. In 2000, the patient received a craniocerebral injury in a car accident, received no timely treatment. Family history: the patient is divorced, has one healthy daughter and granddaughter, which she takes from the kindergarten. The mother and native siblings have a similar disease. Objectively: patient with normostenic constitution, height 164, weight 55 kg. Neurological status: vision is reduced (presbyopia), pupils and eye slits are equal. The volume of motion of the orbits is complete, the nystagmus is horizontal in both directions. Less clearly right nasolabial fold. The soft palate is symmetrical in phonation, the voltage is weakened. Reflexes from the soft palate and posterior pharyngeal wall are preserved. She has mild difficulty swallowing solid food rarely. The tongue in the cavity and when protruding along the middle line, atrophy and fibrillation of the muscles there. Reflexes of oral automatism are negative. There are no sharp paresis of the extremities. Tendon and periosteal reflexes from arms and legs are high, uniform from both sides. There are no pathological stop signs. Muscle tone is diffusely reduced. Sensitive violations are not clear. Easy dysmetry and disidiasis. The coordinating tests are performed with intent. A slight tremor of the head during excitement. During the conversation, she smacks her lips. In the Romberg position, the ataxia of the trunk, in tandem is not worth more than 10 s. Gait is ataxic, does not perform 10 consecutive steps in tandem. . Scale for the assessment and raiting of ataxia (SARA) was 16 points. Speech - dysarthria, cerebellar syndrome with mild extrapyramidal insufficiency. A consultation of a psychiatrist was recommended in connection with memory impairment.

III-6 Junior sibs of proband G., born in 1975. The man first applied to the medical genetic consultation on January 19, 2012, he does not present any complaints. From the words of his wife, her husband's speech became slow, the walk became uncertain, there are attacks of dizziness, occasionally choking with saliva during sleep. He applied for donating blood for DNA diagnosis on carrying a mutation in the *DRPLA* gene. Works as a teacher in the center of technical creativity. He is married, has two children, the eldest son from the first marriage of his wife. Head trauma with concussion of the brain in the anamnesis, without adequate treatment. From words, alcohol does not cause. Smokes, 1 pack is enough for 3-4 days. Objectively: asthenic physique, high growth. In neurological status: sight and hearing are preserved. Lachrymation OU. Pupils of rounded shape, equal,

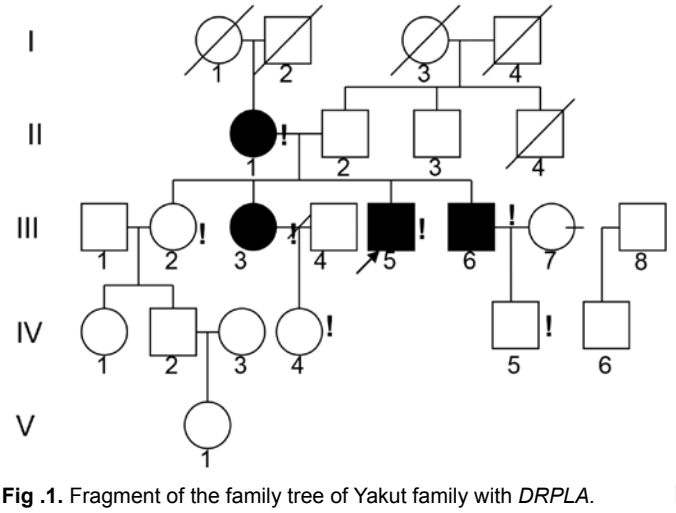

Fig .1. Fragment of the family tree of Yakut family with *DRPLA*.

photoreaction alive. The right eye gap is narrower. The volume of motion of the orbits is complete, nystagmus is absent. Less clearly right nasolabial fold. The soft palate is symmetrical and mobile. Language - a rough deviation to the right, without atrophy and fibrillation. ROA - easy proboscis reflex. There are no sharp paresis of the extremities. Muscle tone is normal. Tendon and periosteal reflexes from the hands and feet of medium liveliness, no difference in sides. When performing a finger-sap sample: on the right it performs uncertainly, on the left it is satisfactory. Easy dysmetry. There may be an easy restriction in the right shoulder joint with the raising of hands upwards, in dilution to the sides (shoulder injury in September 2011). The heel-to-shin test - satisfactory. There are no sensory disturbances. In the Romberg pose, easy rocking. In tandem is <10 seconds. Tandem gait works with difficulty. Scale for the assessment and raiting of ataxia (SARA) was 8 points. Speech is an easy dysarthria. MRI of the brain from 29.02.2012 . Conclusion: MRI-signs of cortical atrophy of cerebellar hemispheres on both sides. Post-traumatic encephalopathy. EEG on 02/07/2012. Conclusion: Unexpected diffuse changes in brain BEA. Focal paroxysmal activity is not present.

IV-5 nephew of the proband, born in 2000. Complaints: increased fatigue. In the clinic: a light pyramidal syndrome. EEG on February 18, 2012 - without any special features.

Thus, the clinical symptoms of DRPLA patients from the Yakut family - ataxia, extrapyramidal and psychiatric disorders - coincide with the literature data on DRPLA and can be attributed to a later debut with a small degree of expansion of CAG repeats.

The conclusion

Among the sample of Russian patients, dentarubroparidotoid atrophy, a rare form of autosomal dominant spinocerebellar ataxia, this pathology was revealed for the first time with the help of molecular genetic methods of diagnosis. Expansion of CAG repeats in the *DRPLA* gene was found in four members of the Yakut family. The proband and mother of the proband had a late form of ataxia, and a mutation in the *ATXN1* gene (SCA 1 type) was first eliminated, followed by other more frequent ataxia types: *ATXN2* (SCA2), *ATXN3* (SCA3), *CACNL1A4* (SCA6), *TBP* (SCA17) . Due to the fact that the mother of the proband is an orphan, was brought up in the Olekma children's home (Yakutia), it is difficult to identify other close relatives of the family. Yakutia is a cluster of accumulation of SCA1 type, and there are also unidentified forms of SCA [2]. In our work, a molecular-genetic method of investigation in 80 patients with unidentified form of SCA excluded a mutation in the genes: *ATXN2* (SCA2), *ATXN3* (SCA3), *CACNL1A4* (SCA6), *TBP* (SCA17).

The clinical symptoms of DRPLA patients from the Yakut family - ataxia, extrapyramidal and mental disorders - coincide with DRPLA literature data and can be attributed to a later debut with a small degree of expansion of CAG repeats [4, 5, 7]. As for other polyglutamine diseases in the Yakut family with DRPLA, there are: reverse correlation between the degree of expansion of the repeats in the mutant allele and the age of manifestation of the symptoms of the disease, a direct relationship between the degree of expansion of repetitions and the severity of clinical manifestations, the phenomenon of anticipation.

Currently, blood pressure in the SCA is becoming particularly relevant, both in the medical and social terms, due to the rather widespread prevalence, difficulties in clinical diagnosis, the absence of an etiotropic treatment method, a steadily progressing course, a high incidence of disability and fatal outcomes. Therefore, the timely identification and direction of patients with cerebellar syndrome in medical genetic counseling, the development of the most effective methods of counseling, including DNA diagnostics, are of great social and economic importance.

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