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FEATURES OF SPINOCEREBELLAR ATAXIA TYPE 17 IN YAKUTIA (CLINICAL OBSERVATION)

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A literature review of the disease type 17 spinocerebellar ataxia (SCA 17) was carried out. The authors present their own clinical observation of SCA 17 with the absence of characteristic signs of SCA - an inverse correlation between the degree of expansion and the age of manifestation of symptoms of the disease, as well as a direct relationship between the degree of expansion of repeats and the severity of clinical manifestations, confirming the existence of differences in the clinical picture of different types of SCA.

Keywords: autosomal dominant spinocerebellar degenerations, expansion of trinucleotide repeats, spinocerebellar ataxia type 17.

Introduction. To date, 47 subtypes of spinocerebellar ataxias (SCA) have been described. SCA is considered a rare group of cerebellar ataxias, with an average prevalence 2.7 cases per 100,000 population. The most common forms are polyglutamine dilatation diseases (ATXN1 / SCA1, ATXN2 / SCA2, ATXN3 / SCA3, CACNA1A / SCA6, ATXN7 / SCA7, TBP / SCA17 , and ATN1 / DRPLA) [2]. Yakutia is a hotbed of SCA1 accumulation in Russia, the prevalence is 46 cases per 100,000 [12]. Spinocerebellar ataxia type 17 (SCA17, MIM 607136) is a severe neurodegenerative disease, a rare variant of ataxia caused by the expansion of trinucleotide CAG repeats in the TBP gene (TATA-binding protein) on chromosome 6q27. The protein product of the gene belongs to transcription factors and specifically binds to the regulatory TATA site of the transcribed segments [6].

The first case of the disease was described in 1999 by R. Koide et al. in a 14-year-old Japanese patient, who, from the age of 6, had impaired coordination of movements and intellect, and then ataxia of the trunk, spasticity, muscle weakness, dysphagia and dysarthria, and atypical absences were added. The patient was found to have an expansion of tandem trinucleotide CAG repeats in the *TBP* gene (63 copies of repeats at a rate of 25–42 repeats) [4]. Later, a similar mutation was found in other families of Japanese and European origin [7, 9, 10, 14, 19]. The age of onset of symptoms is usually 19–48 years, but an extremely severe phenotype of type 17 spinocerebellar ataxia (SCA17) with the onset of the disease at 3 years of age and the maximum number of CAG repeats known to date is 66 copies [4]. Late variants of type 17 spinocerebellar ataxia (SCA17) with manifestation of symptoms at the 7th decade of life are also known. In the examined families with SCA17, there was a clear anticipation, as well as an inverse correlation between the age of disease onset and the number of trinucleotide repeats[25] .

In 2016, S.A. Klyushnikov et al. identified the first case of SCA 17 in the Russian population [2]. The gene responsible for the development of the disease encodes the TATA-box-binding protein; therefore, it was named *TBP* (TATA-binding protein) [7]. The site with microsatellite CAG / CAA repeats, the expansion of which causes the development of the disease, is located in exon 3. The range of normal values for the size of the polyglutamine site in the protein is between 25 and 44 amino acid residues. Alleles causing the development of the disease contain 43–63 CAG / CAA repeats. In this case, the level of expansion of 43–49 repeats is considered a zone of incomplete gene penetrance. In a patient - a man of 27 years old, suffering from a real disease for 7 years, a heterozygous carriage of a mutant allele in the *TBP* gene with a number of CAG / CAA repeats of 45 was revealed. disease caused by a mutation with incomplete penetrance (the number of CAG / CAA repeats is less than 49). Such a disease did not occur in the patient's family, however, during DNA diagnostics of the parents, an identical mutant allele was found in the patient's healthy mother, which clearly demonstrates the phenomenon of incomplete penetrance of the mutation in this molecular form of AD-CCA. Subsequently, the presence of SCA 17 was found in 2 more families [2].

Clinical features. Spinocerebellar ataxia type 17 is a neurodegenerative disease with an autosomal dominant mode of inheritance, with extensive phenotypic variability and age at the beginning of several decades. The main clinical manifestations, as for other types of ataxia, are impaired coordination of movements due to damage to the structures of the cerebellum, as well as its afferent and efferent connections, and dementia [25].

In this literature review, patients with SCA17 (Tab.) ranged from 3 to 60 years of age at onset, and about half of the patients developed ataxia as an initial symptom. The age of onset of the disease weakly correlated with the age of the number of repeats (Tab.) [25]. During the course of the disease, the majority of patients (> 90%) developed ataxia, which was manifested by gait instability and speech impairment. Cognitive dysfunctions and memory impairment were also observed as an initial symptom [20]. Dementia is the second most common symptom (73%) during the course of the disease. In childhood - dementia. Psychiatric symptoms such as aggression [16], paranoia [8], euphoria [24] and depression [17, 22] are common. Behavioral disorders or personality changes can be diagnosed as mental disorders. Involuntary movement is one of the characteristic features of SCA17 [13, 18]. Since chorea is a well-known symptom of SCA17, the clinical phenotype sometimes overlaps with Huntington's disease (HD) and is characterized by the triad of movement

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disorder, mental manifestations, and cognitive impairment [27]. In many cases of clinically suspected HD, patients lack the CAG re-expansion that causes HD. It is believed that such people suffer from HD or HD-like phenocopy syndromes. disorders [25, 26]. Therefore, SCA17 is also called Huntington's disease.

The relationship between the number of repetitions and clinical symptoms of SCA17. Previously, Japanese scientists investigated the relationship between the number of repetitions and clinical symptoms and found that more than 75% of patients with a CAG / CAA repeat size of 43-50 had intellectual impairment; in some people, intellectual problems and involuntary movements were the only signs. Psychiatric problems or dementia, parkinsonism and chorea, a clinical combination similar to Huntington's disease, are more common in people with CAG / CAA repeats in this range than in people with more repeats. All people with a CAG / CAA repeat size of 50-60 have ataxia and 75% have decreased intellectual function. Pyramidal signs (eg, increased deep tendon reflexes) and dystonia are more common in these people than in people with fewer repetitions. These features are confirmed in this literature review. (Tab.) [23]. Two children were reported with more than 60 repetitions. One, family case, with a 66 repetition extension of CAG / CAA, a gait disorder developed at age 3, followed by spasticity, dementia, and psychiatric symptoms [16]. Another, with a de novo CAG / CAA expansion of 63 repetitions, developed ataxia, an intellectual impairment at age 6, followed by spasticity [4].

Less common symptoms are epilepsy [3, 4, 8, 9, 14, 19, 22] (20%), vegetative symptoms [9, 10, 11, 24] (9%), apraxia [9] (7%) and symptoms of peripheral nerve damage [3, 17, 22] (3%). Lin et al. [22] reported a patient who developed ophthalmoplegia with parkinsonism and Rolfs et al. [8] reported a patient with symptomatic hypogonadism.

CT and MRI in patients with type 17 spinocerebellar ataxia (SCA17) of the hemispheres show gross cerebellar atrophy and less pronounced cerebral atrophy [4]. The section reveals a general decrease in the volume and mass of the brain, microscopically - the death of neurons and gliosis in the region of the caudate nucleus, shell, thalamus, inferior olives, frontal and temporal cortex. In the cerebellum, there is degeneration and death of Purkinje cells, growth of Bergmann's clays. Immunohistochemical analysis reveals intranuclear neuronal inclusions typical of polyglutamine diseases, containing ubiquitin and polyglutamine epitopes [7, 9, 19].

Thus, there are several characteristic differences between SCA17 and other polyglutamine diseases.

First, SCA17 exhibits a complex and variable clinical phenotype, in some cases overlapping the phenotype of Huntington's disease.

Second, compared to other subtypes of SCA caused by increased trinucleotide repeats, expectation in the relationship of SCA17 is rare due to the characteristic structure of the TBP gene.

Third, SCA17 patients often have diagnostic problems that can arise from nonpenetrance. Since the gap between normal and abnormal repeat numbers is very small, it is difficult to determine the threshold for the number of abnormal CAG repeats in SCA17.

Clinical case. A woman of Yakut nationality, 49 years old, retired in service in the Ministry of Internal Affairs, was hospitalized in the neurological department at the end of 2019 at the Hospital of the Yakut Scientific Center of the CMP with complaints of impaired coordination, ataxic gait, speech impairment, general weakness, rapid fatigue, decreased vision, constant dizziness of a non-systemic nature, lowering blood pressure to 90/60 mm Hg, pain in the right knee joint, difficulty in bending the legs in both knee joints, apathy, depression, irritability, sleep disturbance, cannot fall asleep, falls asleep in the morning.

From the anamnesis of the disease: the first manifestations of the disease appeared in 2014 at the age of 44. When turning the head, dizziness appeared, thought from cervical osteochondrosis, gait slowed down, could not run. During the year, speech and gait disorders gradually appeared, colleagues at work noticed. She was examined and treated in the neurological department of the medical unit of the Ministry of Internal Affairs, then in the neurological department of the Republican Hospital №2- - EMP with a diagnosis of Cerebellar syndrome. In 2015, she underwent DNA diagnostics for the carriage of a mutation in the *ATXN1* gene (26/27) at the Medical Genetic Center Republican Hospital №1-NCM, SCA type 1 was excluded. In 2016, in the same place, the patient's DNA was checked for the carriage of mutations in the genes *ATXN2* (20/27 repeats), *ATXN3* (22/29 repeats) and in the gene *TATA-binding protein (TBP*), as a result of determining the size of alleles on an automatic DNA analyzer ABI Prism 3500 (Applied Biosystems) identified 35/65 repeats of the 6q27 locus in the *TATA-binding protein (TBP)* gene, normally 29-42 repeats. Gradually the disease progresses. I started walking with a cane 2 years ago. Decreased mood since last year, could lie for days, not eat. Sleep disturbances appeared in late spring 2019, took glycine, before that tenoten, became less irritable, was touchy, tearful. For the last year he has not moved independently on the street, only with an accompanying person on one side. Disability 2 g since 2018, b / s. She underwent treatment in neurological department of Republican Hospital №2- - EMP in September 2019, without positive dynamics, she began to stagger more. He does not know the pedigree from his father's side, his mother told me that she met in Tiksi. The mother died of three ischemic strokes in 2010 at the age of 65. She was born the first child of two in Pokrovsk. Has a brother, is clinically healthy. She grew and developed with age. Has two secondary specialized educations, a paramedic and a lawyer. She worked in the police as an inspector for administrative law. Divorced, 1 son, adult, DNA diagnostics did not pass. She lives alone in Pokrovsk, in a partially furnished house with central heating. He cannot cope with the household, a social worker comes. The son wants to take him to Yakutsk, the patient does not want to be a burden. Past illnesses: he does not know childhood infections, hepatitis during pregnancy, Tuberculosis, diabetes mellitus, stroke, he denies head trauma. In 2015, under general anesthesia, uterine polyps were removed in 2015 under general anesthesia. Gynecological history: P-3, m / abortions - 2, childbirth - 1, natural. She is allergic to household dust, animal hair in the form of a runny nose, sore throat. I used to smoke.

Neurological status: clear consciousness. It is oriented correctly in time, space and self. The behavior is adequate. The mood background is slightly lowered. FMN: distinguishes smells, vision is reduced due to presbyopia. The eye slits are equal. Pupils are rounded, equal, FTR is reduced. The movement of the eyeballs is slightly limited in the extreme abduction. Nystagmus is horizontal and more vertical. There is no diplopia. The exit points of the trigeminal nerve are painless. The sensitivity on the face is not disturbed. The nasolabial folds are symmetrical. Hearing saved. The pharyngeal reflex is triggered. There is no dysphagia. Tongue in the midline, agitated with fasciculations at the edges. Dysarthria is mild, without chanting. ROA Marinescu-Radovici ++. Flaccid tetraparesis. Hand dynamometry on the right is 18 kg, on the left is 13 kg. The tone is diffusely

Brief clinical signs of patients with SCA 17.

1	2	3	4	5	6	7	8	9	10	11
Sex	Age of onset	Initial symptom	Ataxis	Dementia	Involuntary movement	Pyramidal signs	Extra py-ramidal signs	Psychiatric symptoms	CAG \CAA	References
F	60	chorea	-	nc	Chorea	-	nc	depression	41	Park et al. [5]
F	35	Gait instability	н/д	nc	Chorea, trunk titubation	+	+	depression	41	Herrema et al. [20]
M	59	Slurred speech	+	nc	mioclonus	-	-	-	41	Dohertyet al [11]
M	42	Reduced operating speed	+	++	-	+	+	nc	43	Nielsen et al. [21]
F	29	Gait instability, behavior change	++	+	Chorea	+	-	-	44	Stearinet al. [13]
M	48	Gait instability	+	+++	Dyskinesias	nc	nc	nc	44	Mariottiet al. [22]
F	40	Gait instability	+	nc	nc	nc	nc	nc	44	
F	38	Gait instability	+	nc	nc	nc	nc	nc	44	
M	41	behavior change	+	+	Dyskinesias	+	nc	nc	45	
F	38	depression	nc	+++	nc	+++	nc	depression	45	
F	40	Gait instability	+	+	Dyskinesias	nc	nc	nc	45	
м	34	Gait instability	+	-	Dyskinesias, tremor	+	nc	nc	45	
м	55	Chorea	+	Нет данных	Chorea, Dyskinesias	nc	nc	nc	45	
F	52	Gait instability	+	+	Dyskinesias	nc	nc	nc	45	
м	55	Gait instability	+	+	nc	nc	nc	nc	45	
м	nc	Ataxia, urination disorder	+++	+	-	+	++	Euphoria	45	Lin ett al. [24]
F	30	Speech impairment, depression	+	nc	nc	nc	++	depression	45	Rolfs et al. [9]
M	43	Ataxia	+	nc	nc	nc	nc	depression	45	
F	30	depression	+	+	Dystonia, chorea	+	nc	Depress.,aggression, paranoia	45	
M	23	Speech impairment Ataxia	+	nc	nc	+	nc	-	45	
M	19	Behavioral disorders	+	+	Dyskinesias	nc	nc	nc	46	Mariotti et al [22]
M	37	Paranoia psychosis	+	+	choreoathetosis	+	-	Paranoia psychosis	46	Fujigasakiet al. [8]
F	55	Ataxia, dementia	+	+	-	+	+	nc	46	
nc	40	nc	+	+	Chorea	+	+	nc	47	Nakamura et al. [19]
nc	28	nc	-	+	-	+	+	nc	47	
nc	39	nc	+	+	Dystonia,	+	+	nc	48	
nc	48	nc	+	+	Chorea	+	+	nc	48	
F	38	depression	-	nc	nc	nc	nc	Hallucinations, suicidal attempts	49	Rolfs et al. [9]
F	16	Cognitive impairment, ataxia	+	+++	nc	nc	nc	nc	49	
F	48	Chorea	+	н/д	Chorea	nc	+	paranoia	50	Mariotti et al [22]
м	55	Behavioral disorders	+	+	Dystonia, dyskinesia	nc	nc	nc	50	
м	13	mental retardation	+	+	-	+	+	nc	51	Zuhlke et al. [10]
F	35	depression	+	+	dyskinesia	nc	nc	depression	52	Mariotti et al []
F	25	Paranoia	н/д	+++	nc	+++	nc	Paranoia	53	
F	35	ataxia	+	+++	Dystonia,	nc	nc	++	53	Maltecca et al [14]
м	34	ataxia	+	++	Dystonia,	nc	nc	++	53	
м	23	ataxia	+	++	Dystonia,	+	+	++	53	
F	34	Personality disorders	+	+	nc	+	+	Euphoria	53	Fujigasakiet al. [8]
M	35	Ataxia, psychiatric symptoms	+	+++	Dystonia,, Chorea	+	nc	Aggression. Paranoia	54	Rolfs et al. [9]

End of the table

1	2	3	4	5	6	7	8	9	10	11
M	18	Ataxia, dementia	+++	++	nc	+	nc	nc	54	Rolfs et al. [9]
F	23	Hallucinations	++	+	Dystonia,, Chorea	+	nc	Mania	54	
F	18	Speech impairment	+	nc	nc	nc	nc	-	54	
M	18	Ataxia	+	nc	Dystonia	nc	nc	-	54	
F	20	dystonia	+	-	Dystonia corticollis	-	-	nc	55	Zuhlke et al [10]
nc	19	nc	+	+	dystonia	+	+	nc	55	Nakamura et al. [19]
nc	25	nc	+	+	dystonia	+	+	nc	55	
F	6	Mental retardation, ataxia	+	++	-	+	-	nc	63	Koide et al.. [4]
F	3	Ataxia	+	+++	dystonia	+	+	++	65	Maltecca et al. [14]

reduced. SPR from arms and legs alive, equal. In the Romberg position, stands with legs together, but with pronounced ataxia. Falls in tandem. The finger test is performed with light intention on both sides. A knee-calcaneal test with moderate ataxia on both sides. There are no meningeal symptoms. There are no sensitive violations. Gait is ataxic, with a cane; on the right, the legs are raised in a semicircle. There are no pelvic disorders.

The patient underwent studies on the following scales:

Morse fall assessment sheet from –60 points (high),

Ataxia scales: SARA -15 points from 12/09/19 and 12.5 points from 12/19/19, positive dynamics, decrease by 2.5 points (maximum 40 points).

ICARS - 25 points (maximum 100 points).

Hospital Anxiety and Depression Scale (HADS): Anxiety - 3 points, Depression - 7 points, where 0-7 points are normal, 8-10 points - subclinically expressed anxiety / depression.

The Montreal Cognitive Assessment Scale - 23 points (norm 30 points). On the attention test, the patient did not cope with serial subtraction and with one of the lists of numbers. There was also a decrease in memory in the stitched work.

A.M. Wayne assessment of vegetative changes – 39 meaning a pathological increase in points (the norm is up to 15 points). The sympatatonic variant of the vegetative tone prevailed.

According to instrumental studies: *ECG* from 10.12.19: Rhythm - sinus with a heart rate of 81 beats per minute. Metabolic changes in the myocardium of the lower-lateral regions.

Spirography from 10.12.19 conclusion: lung capacity within normal limits. Indicators of airway patency at the lower limit of the norm.

Electroneuromyography, conclusion: SPI on the motor fibers of the median, ulnar, tibial nerves on the right and left without pathology, peroneal nerves on the right and left reveals moderate axonal disorders at the distal level in the form of a decrease in the amplitude of the M-response by 55.5-62% (more pronounced on the left).

SPI on the sensory fibers of the median, ulnar and peroneal nerves on the right and left - without pathology.

The F-wave along the motor fibers of the ulnar nerve on the right reveals signs of reinnervation in the form of repeated waves up to 15.4%.

F-wave along the motor fibers of the ulnar nerve on the left, median, tibial nerves on the right and on the left - without clinically significant disorders. In the clinical aspect, there are signs of symmetric motor axonal neuropathy on the distal segments of the peroneal nerves of a moderate degree.

EEG from 09/23/2020. Conclusion: general characteristics of EEG at rest: a low-amplitude EEG is recorded. Significantly disorganized alpha activity is observed in the form of separate waves of medium amplitude, low index, irregular, most pronounced in the frontal region. No amplitude modulation. Beta-activity dominates in the form of a rhythm of a high index, medium amplitude, low frequency, with an area of expression in the anteroposterior region (Fp1 Fp2).

MRI of the brain from September 24, 2019 revealed a small congenital retrocerebellar cyst and an expansion of the cerebellar grooves, probably as a manifestation of atrophic changes.

In the hospital, the following consultations were held: ophthalmologist from 10.12.19 D: Vertical nystagmus. OI hypertensive angiopathy.

Psychiatrist from 12/11/19D-z: Anxiety-subdepressive syndrome.

Physiotherapist on 11/12/19 prescribed massage of the lower extremities.

Clinical psychologist from 12/13/19 Endorsement: Reduced emotional background, experiences in connection with the disease, aggravated by a feeling of loneliness. General bypass with bypass with deputy.

Geneticist 12/18/19 Cerebellar ataxia, late form, unspecified type of inheritance. Type 17 - SCA 17 is not excluded. Progressive course, flaccid tetraparesis, cerebellar syndrome. The offspring risk for late cerebellar ataxia is high.

Treatment performed: Aminoplasmal 250.0 intravenous drip slowly, after 2 days No. 5 - a course of amino acids for basic diagnosis, Mexidol 5.0 intravenous cap No. 10 for antioxidant therapy, Atoris 20 mg in the evening, Phenibut 250 mg 1 ton at night , Grandaxin 50 mg 1t * 2rvd (y, d), Vit B12 i / m, exercise therapy. massage of the lower extremities.

Against the background of treatment, he was discharged with some improvement, in the form of a decrease in intention when performing coordination tests, the speech became slightly clearer.

Conclusion. Thus, SCA17 is considered to be a complex and variable clinical phenotype, in some cases overlapping the phenotype of Huntington's disease. Compared to other subtypes of SCA, caused by increased trinucleotide repeats, expectation in the relationship of SCA17 is rare due to the characteristic structure of the TBP gene. SCA17 patients often have diagnostic problems that can arise from nonpenetrance. Since the gap between normal and abnormal repeat numbers is very small, it is difficult to determine the threshold for the number of abnormal CAG repeats in SCA17.

The clinical case described in the work

confirms that SCA 17 is a clinically and genetically heterogeneous disease. In this case, we do not observe an inverse correlation between the degree of expansion and the age of manifestation of symptoms of the disease, as well as a direct relationship between the degree of expansion of repeats and the severity of clinical manifestations. We also observe differences in the clinical picture of SCA 17 in this case and SCA 1, which is widespread in Yakutia, which is also important for differential diagnosis between these two hereditary ataxias to determine the prognosis of the disease and the degree of risk of gene mutation transmission to offspring.

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