Differential Diagnosis of Kennedy Spinal-Bulbar Amyotrophy and Familial Form of Motor Neuron Disease in the Republic Sakha (Yakutia)

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ABSTRACT

In a result of clinical and epidemiological and genetic studies of the motor neuron disease in Yakutia, according to the register of the neurological department of Belarus № 2 for the period 1989-2013 1 MND family event was identified and 3 patients with spinal - bulbar amyotrophy Kennedy. The complexity of the differential diagnosis between these diseases has been very difficult on the clinical stage of diagnosis, because in all cases isolated lesion of peripheral motonevrona characteristic of both diseases was found.

Keywords: motor neuron disease (MND), amyotrophic lateral sclerosis (ALS), progressive muscular atrophy (PMA), spinal- bulbar amyotrophy Kennedy.

INTRODUCTION

Spinal- bulbar amyotrophy Kennedy is the main condition, which is necessary to differentiate the MND family event. Taking into account the issues of bioethics in the diagnosis of MND established diagnosis of spinal- bulbar amyotrophy for the patient becomes relatively favorable than the diagnosis of ALS.

Spinal- bulbar amyotrophy Kennedy or Kennedy 's disease (MIM 313200) - this is a rare neurodegenerative disease X-linked recessive mode of inheritance, which manifests itself in men in a relatively late age, usually after age 40. The disease was first described by Kennedy [et al.] in 1968. The clinical picture of the disease presented symptoms of peripheral motor neuron and is manifested by weakness and muscle atrophy in the proximal and distal extremities with fascicular twitching and bulbar impairment. In addition to these symptoms this disease is characterized by endocrine disorders, such as gynecomastia, infertility, testicular atrophy. Despite the late onset disease is characterized by slowly progressive course with very high life expectancy [12]. The incidence is - 1 in 40 000 men [13]. Kennedy disease is caused by damage of the androgen receptor (AR), located in the Xp11.2- 12 locus [6]. Mutation is the expansion of tandem repeats in the CAG- 1 exon gene AR. The normal number of copies of CAG is 10-36, while Kennedy amyotrophy patients have an increased number of tandem repeats - from 38 to 72. [11]. Considering Kennedy disease debut in later life and the electoral defeat of peripheral motor neuron, the disease is difficult to diagnose based only on clinical symptoms, because

conducting molecular diagnosis of the disease is possible in health care settings, with molecular genetics laboratory.

The differential diagnosis of spinal- bulbar Kennedy amyotrophy and ALS needs to be considered in the clinical picture of disease presence or absence of symptoms referable to the central motoneuron, loss of peripheral motor neuron disease lack of dependence on the sex of the patient is characteristic of ALS, a progressive disease course (fast and slow ALS disease in Kennedy), as well as rare hereditary abnormalities occurring in ALS. Unlike ALS, the presence of clinical symptoms of the electoral defeat of the peripheral motor neuron only, male sex, and endocrine disorders such as infertility, gynecomastia, testicular atrophy can be suspected spinal-bulbar amyotrophy Kennedy, even in the absence of family history. Although the particular difficulties can be found if the patient has a «false negative " family history, when a patient has no communication with relatives in both cases. In the diagnosis of Kennedy's disease may also help the relatively slow progression of the disease, in contrast to ALS.

For motor neuron disease (MND) are severe neurodegenerative disease of unknown etiology and pathogenesis unspecified , which is characterized by the selective loss of central and peripheral motor neurons and progressive course , invariably leads to death. According to the International Classification of Diseases - X (ICD - X, 2003), are a group of MND family motor neuron disease, amyotrophic lateral sclerosis (ALS), primary lateral sclerosis (PLS) , progressive bulbar palsy (PBP) and progressive muscular atrophy (PMA). The basis of this classification is the concept of the unity of the pathogenesis of bulbar, spinal central and peripheral motor neurons and CBE, FSN and ACA treated as isolated lesion of the central or peripheral motor neuron. The most common of this group in the world is amyotrophic lateral sclerosis (ALS), which accounts for 80 % of all other diseases, PMA -9 %, 8% of PRP - and PlS- 2% [5].

In clinical practice, due to the lack of a specific test and a variety of diseases that are accompanied by a syndrome of ALS diagnosis MND for neurologists is very challenging. The diagnosis of ALS is currently mainly clinical, as there is no specific marker and the data of laboratory and instrumental examination methods are complementary to clinical assessment of motor disorders that often creates difficulties in diagnosis, especially in the early stages of the disease. In favor of ALS in the early stages of the pathological process may indicate violations of respiratory function, dysarthria and dysphasia, which cannot be explained by other causes.

In 5-10% of all ALS patients are family cases [7, 9]. About monogenic inheritance of the disease among relatives a positive family history testifies. Family ALS cases can be transmitted as an autosomal dominant, autosomal recessive or X-linked pattern of inheritance. X - linked

dominant MND was found in a large American ancestry [15]. Different types of inheritance MND say about its genetic heterogeneity. To date, at least 12 chromosomal loci associated with the development of autosomal dominant, autosomal recessive, or X-linked forms of ALS as well as some ALS -like syndromes are identified. To half of these forms genes and their protein products are set [3]. Familial ALS, according to the clinical features and course of the disease, can be subdivided into two distinct subgroups: 1) "classic" late-onset ALS is inherited in an autosomal dominant manner and is associated with nine independent chromosomal loci 2) "juvenile» ALS with the manifestation of symptoms in adolescence) juvenile ALS is characterized by the onset of disease is most often on the 2nd decade of life, the variable ratio of expression of central and peripheral motor neurons, as well as a very slow progression, in some cases does not affect the natural life span [14]. Juvenile ALS can be inherited in an autosomal dominant and autosomal recessive manner.

Clinical manifestations and morphological changes in sporadic and familial forms generally have a similar picture, but in general for the familial forms of the disease, the clinical picture is characterized by several symptoms earlier debut [1].

Approximately 20% of patients with familial forms of ALS disease is caused by mutations in a gene located on chromosome 21q 21 and encoding cytosolic enzyme Cu / Zn superoxide dismutase (SOD1) [2]. This locus and the corresponding form of ALS were designated ALS1. According Andersen PM [1], underdiagnosis of familial ALS can artificially lower because of low penetrance gene SOD1, due to the lack of collected family history or " “false-negative” family history in the case of loss of communication between the different branches of the same family, the reluctance of family members to recognize hereditary nature of the disease, the death of family representatives, who were carriers of the gene from other causes of ALS at an earlier age, ALS underdiagnosed in earlier generations, the presence of illegitimate children in families.

Variability of forms of the disease within families was marked. Very rarely in patients within the same family one and the same form of ALS was described. The development of progressive muscular atrophy, classical ALS, progressive bulbar palsy, and primary lateral sclerosis, even within the same family is probable [10]. According to some studies intra-variability of ALS is even superior inter-family [8].

The next group of disease MND, which are encountered in doctor’s practice, is progressive muscular atrophy. First family event PMA was described in 1850 by F.Aran. He called this disease progressive muscular atrophy. In the described case, the patient, his sister and

two uncles of his mother died from the disease, which is characterized by atrophy, paresis of muscles of the upper and lower extremities. Around the same time, A. Duchenne described a similar syndrome, which was accompanied by progressive muscle weakness. Later, J.M. Charcot called PMA named it after both researchers Duchenne - Aran disease [11]. In 1880 W.Oster described progressive muscular atrophy in 13 patients in two generations of one family [1]. Absence of clinical PMA endocrine disorders, rapid progression of the disease, and the absence of hereditary factors suggest the possible PMA. But the decisive role belongs to direct DNA diagnosis, which in the case of spinal- bulbar amyotrophy Kennedy reveals increase trinucleotide CAG - repeats in the androgen receptor gene AR.

MATERIALS AND METHODS

Since 2006 all patients with MND entered in the register of the neurological department of Republican hospital № 2 with questioning and filling neurodevelopmental card followed by molecular genetic diagnosis to avoid Kennedy disease. Molecular genetic testing is carried out in the molecular genetics laboratory Genetic counseling (MGC) of the Republican hospital №1- National Center of Medicine (NCM). During the period from 1989 to 2013 130 patients with MND were included into Register.

RESULTS AND DISCUSSION

As a result of clinical and epidemiological studies according to the register of the neurological department of Republican hospital № 2 we revealed 113 or 86.9 % of patients with ALS; 13 patients with PMA (10 %); PLS 5 patients (3.8 %) and 2 patients with PRP (1.5%). 1 family event and 3 cases of MND spinal- bulbar amyotrophy Kennedy were revealed. According to the MGC NCM, Yakut three unrelated families in which it was revealed 7 patients with Kennedy disease, are under Neurogeneticist supervision [4].

At filling neurodevelopmental card in the test case of family MND autosomal dominant inheritance from the father in the three children from six (proband and his two older sisters) was established: All patients were diagnosed clinically MND in the neurology department of the Republican hospital № 2, except for father, who died at age 52 and at the time of addressing his son to medical facility, he was not alive. From the stories of relatives, he two years was bedridden because could not walk due to weakness in the legs, swallowed badly, suffered excessive salivation, his speech was slurred, at the end of his life he lost it. In youth he had pulmonary tuberculosis. There was no information about the other relatives from the father and mother sides. The family believed that their father died from lung cancer, because before his death he had dyspnea: slept in a semi-sitting position, could not cough up phlegm and spitting.

In the clinical picture of all patients with the family MND isolated lesion of peripheral motoneuron is noteworthy, which is manifested by areflexia, atony and bulbar disorders without sensitive and pelvic disorders, and early onset of the disease with a slow progression of the disease. In the clinical case in the proband the first symptoms appeared at age 32, when he noticed the weight loss of hands, their shaking, and body muscle twitching. Bulbar disorders joined only after 10 years. In total duration of disease was 14 years. In older of two sisters disease debut manifested itself in 40 years, when she began to complain of weakness in the legs: having trouble in climbing the stairs and into the bus. Gradually weakness in the hands joined, atrophy of hands, feet appeared, there were fascicular twitching and bulbar disorders. During the last 2 years of life, she was bedridden, unable to move independently, roll over in bed; she could not eat because of swallowing disorders. She died at the age of 48. Disease duration was 8 years. The younger sister, born in 1950, lives constantly in one of the republics of the CIS, and occasionally travels to relatives in Yakutia. She became ill at the age of 50 years. The disease began as well as his older sister with weakness in the legs, began to move slowly, climbing stairs with difficulty, could not hold a spoon in hand, cup and other items. There was atrophy of the hands and feet, slurring of speech appeared. Currently, the clinical picture of the disease in this patient appears with sluggish deep proximal tetraparesis, distal tetraplegia and moderate bulbar disorders without pelvic and sensory disorders. She moves in a wheelchair with the accompanying. Duration of her disease is today 14 years. All members of the described family are of Yakut ethnic group and are natives of Hangalassky area, which belongs to the Central region.

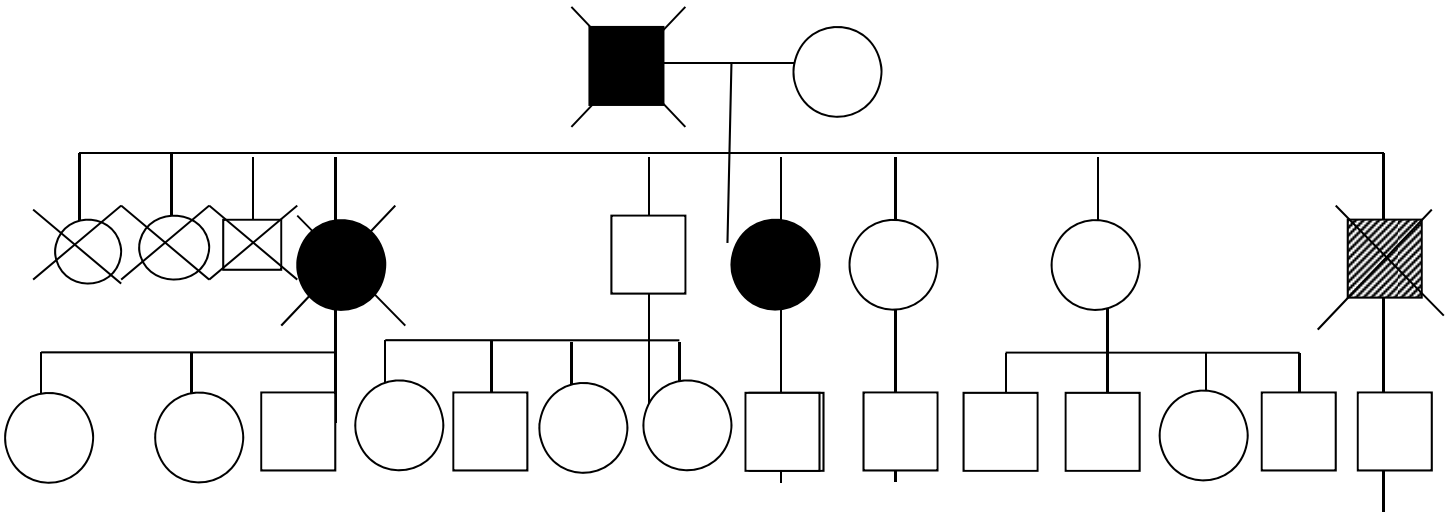

Fig. 1. Ancestry of a patient F., born in 1961, with a family MND

Fig. 1 shows that the disease is transmitted in an autosomal dominant pattern of inheritance from the sick father. From six adult children three children are diseased: two sisters and a younger son. Three older children died in infancy from a few months to 1.5 years. Characteristic of this family event is a relatively early onset of the disease, the lack of symptoms referable to the central motoneuron and relatively long duration of the disease with a slow progression that is not characteristic of ALS. These symptoms allow suggesting in the diseased members of this family a rare disease of MND groups - progressive muscular atrophy (PMA) or disease Duchenne - Aran.

Figure 2. Patient V., 72, with progressive muscular atrophy

In our practice in Yakutia a man, who was observed with ALS for 2 years in the neurology department of the Republican hospital № 2, was diagnosed with spinal- bulbar amyotrophy Kennedy in 2004. It was the first clinical diagnosis of SPA in Yakutia. The diagnosis of spinal - bulbar amyotrophy Kennedy was installed after the introduction into clinical practice of molecular genetic diagnostics at the National Center of Medicine in Yakutsk.

In total from the patients referred from different regions of the Republic to the neurological department of the Republican hospital number 2, suspected for MND, since 2004 according to the register 3 cases of spinal- bulbar amyotrophy Kennedy were identified. All patients underwent direct DNA diagnosis, which revealed the expansion of trinucleotide tandem repeats gene CAG- AR. The debut of the disease was observed from 44-56 years, with the development of total muscle fatigue in normal physical activities. 5-6 years later joined paresis mimic muscles with fasciculations of the facial muscles and bulbar disorders as choking, dysarthria, atrophy and fibrillation language flaccid tetraparesis with low reflexes. From endocrine disorders two patients were experiencing gynecomastia, infertility, one patient had early extinction of reproductive function.

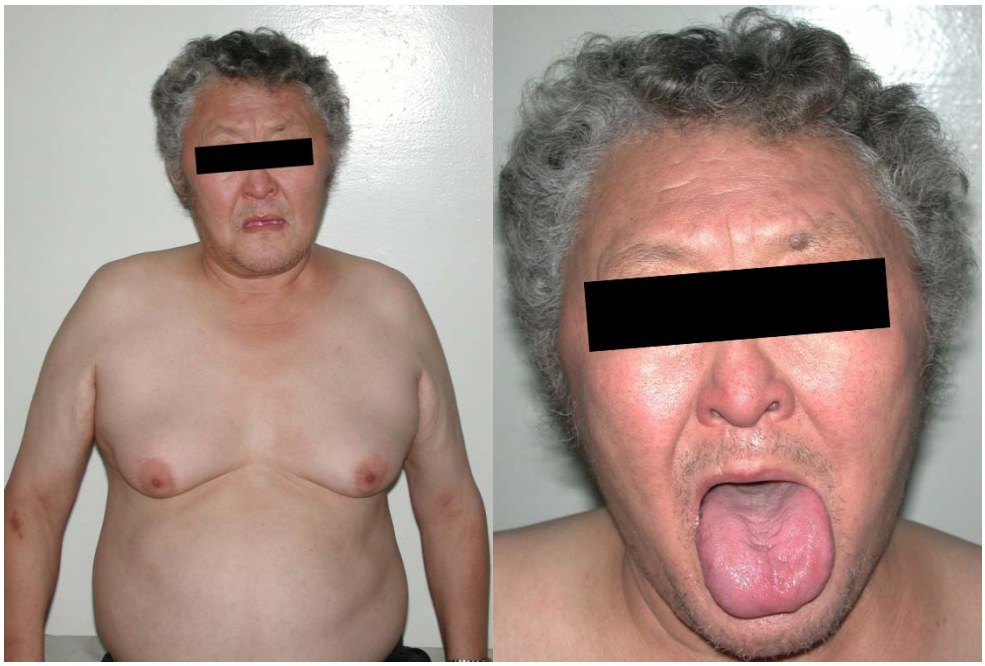

Figure 3. Photo of a patient with X-linked bulbar - spinal amyotrophy. Visible muscle wasting of the shoulder girdle, gynecomastia and tongue with signs of atrophy.

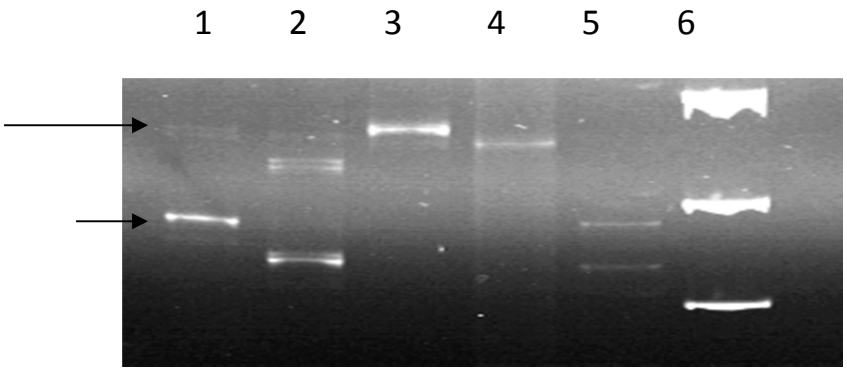

Figure 4. Electrophoregram of patient with Kennedy's disease

Direct DNA diagnosis of spinal - bulbar amyotrophy Kennedy. Electrophoregram 8% polyacrylamide gel: lane 6 - marker puc 19 / MspI, track 3.4 - patients with spinal-bulbar amyotrophy Kennedy, lane 2 - heterozygous carrier of the mutation (relative),

Lane 1, 5 - healthy. Long arrow marks the mutant allele (expansion CAG - repeat androgen receptor gene), a short arrow - the normal allele.

CONCLUSION

Thus diagnosis of familial forms of MND and Kennedy spinal- bulbar amyotrophy represented an important issue, because lack of specific clinical marker for the presence of MND and molecular genetic laboratory only in major medical centers and research institutes, create difficulties in the clinical diagnosis and molecular genetic studies. Study of molecular genetic basis of familial MND is a promising direction for understanding the mechanisms of disease development and requires further studies to identify the genotype of hereditary predisposition to the disease.

REFERENCES

1. Andersen P.M. Genetika bokovogo amiotroficheskogo skleroza [Genetics of amyotrophic lateral sclerosis] Zhurn. nevrologii i psihiatrii im. S.S. Korsakova [J Neurology and Psychiatry SS Korsakov], № 3, 2001, Pp. 54-63.

2. Bokovoj amiotroficheskij skleroz: ruk. dlja vrachej [Amyotrophic lateral sclerosis: manual for Physicians] / Pod red. I.A. Zavalishina [Ed. I.A. Zavalishin]. Moscow: Evrazija, 2007, 447 p.

3. Illarioshkin S.N. Ivanova - Smolenskaya I.A. Markova E.D. DNK-diagnostika i mediko-geneticheskoe konsul'tirovanie v nevrologii [DNA diagnosis and genetic counseling in neurology]. M0scow: MIA, 2002, 591p.

4. Korotov M.N. Maksimova N.R. Nikolaeva I.A. Stepanova S.K. Bolezn' Kennedi v Jakutii [Kennedy 's disease in Yakutia] Sovremennye aspekty jepidemiologii, diagnostiki i lechenija nevrologicheskih zabolevanij na Severe: materialy mezhregion. nauch.-prakt. konf. [Modern aspects of epidemiology, diagnosis and treatment of neurological diseases in the North: materials of the interreg. scientific-practical conf.]. Yakutsk, 2008, Pp. 64-65.

5. Skvorcova V.I., Limborskaja S.A., Levickij G.N. Sovremennye predstavlenija ob jetiologii, patogeneze i lechenii bolezni dvigatel'nogo nejrona [Modern views on the etiology, pathogenesis and treatment of motor neuron disease] Zhurn. nevrologii i psihiatrii im. S.S. Korsakova [Zh. Neurology and Psychiatry SS Korsakov]. 2005, № 1, Pp. 4-12.

6. La Spada A.R., Wilson E.M., Lubahn D.B., Harding A.E., Fischbeck K.H. Androgen receptor gene mutations in X-linked spinal and bulbar muscular atrophy. Nature 1991. N352.- P.77-79.

7. Brown, R.H., Jr. Amyotrophic lateral sclerosis: recent insights from genetics and transgenic mice // Cell. 1995. V. 80. P. 687-692.

8. Chio A., Brignolio F., Meineri P., Schiffer D. Phenotypic and genotypic heterogeneity of dominantly inherited amyotrophic lateral sclerosis. Acta Neurol Scand 1987;75: 277-282.

9. Rowland, L.P. Hereditary and acquired motor neuron diseases. In Merritt's textbook of neurology. L.P. Rowland, editor. Williams & Wilkins. Philadelphia, Pennsylvania, USA. 1995. P. 742–749.

10. Appelbaum J.S. Roos R.P.. Salazar- Grueso E.F. et al. Intrafamilial heterogeneity in heriditary motor neuron disease. Neurology 1992; 42;10: 1488-1492.

11. Amato A.A., Prior T.W., Barohn R.J. et al. Kennedy s disease: a clinicopathologic correlation with mutations in androgen receptor gene. Neurology 1993; 43: 791-794.

12. Kennedy, W. R.; Alter, M.; Sung, J. H. Progressive proximal spinal and bulbar muscular atrophy of late onset: a sex-linked recessive trait. Neurology.- 1968. -N18.- P. 671-680.

13. Andrew S.E., Goldberg Y.P., Hayden L. et al.. Rethinking genotype and phenotype correlations in polyglutamin expansion disorders. Hum. Mol.Genet.- 1997.-N6.- P.2005-2010.

14. Siddique T., Deng H.-X., 1996 Siddique T., Deng H.-X. Genetics of amyotrophic lateral sclerosis // Hum. Mol. Genet. 1996. Vol. 5. P. 1465-1470.

15. Siddique T, Hong ST, Brooks BR et al. X-linked Dominant locus for late-onset familial amyotrophic lateral sclerosis. Am Soc Hum Genet Meeting 1998, Oct, Abstr 1785.

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