O.G. Sidorova, S.K. Kononova, F.A. Platonov, N.A. Barashkov, S.A. Fedorova, E.K. Khusnutdinova, V.L. Izhevskaya

ANALYSIS OF REPEATED CASES OF PRENATAL DNA TESTING OF SPINOCEREBELLAR ATAXIA I IN YAKUTIA

ABSTRACT

The article presents an analysis of the repeated cases of the treatment in families burdened with spinocerebellar ataxia type 1 for the period over 10 years as a widespread rapidly progressive neurodegenerative hereditary disease, representing a specific medical and social problem in the Republic of Sakha (Yakutia). The analysis of the episodes of the repeated treatment for the prenatal DNA testing will allow to determine the competent tactics of medical care for burdened families who are at risk.

Keywords: hereditary diseases, spinocerebellar ataxia type 1, prenatal diagnostics, prenatal DNA testing.

INTRODUCTION

Spinocerebellar ataxia type 1 (SCA1) is a frequent hereditary neurodegenerative disease in Yakutia that has a dynamic mutation characterized by the prevalence of cerebellar signs, brisk tendon reflexes, presence of florid pyramidal signs, frequently with optic and oculomotor nerves damage and speech disorder [1, 2].

Infection rate of SCA1 in Yakutia doubled while reaching 46 cases for 100000 people during the last 21 years. Age of the disease onset closely correlates with the amount of CAG triplet repetitions in mutant gene [9, 11]. Besides that, therewere shown most of the patients with the repeated low-level numbers (39-55) survived to their reproductive years.

Inheritance of dynamic mutations in population is characterized by various degree of a penetrance, an anticipation phenomenon and a clinical polymorphism [1, 2, 5]. Primary medico-genetic consultation, presymptomatic and prenatal testing of the families with SCA1 are accompanied by numbers of the bioethical problems [4].

Thus, in the absence of radical methods of treatment, SCA1is an intractable problem of the regional Genetics Service as the most widespread neurodegenerative disease in Yakutia. This situation raises an issue about the opportunities and prospectsfor primary prevention of SCA1 in the Republic of Sakha [3, 4]. The repeated cases of treatments for thep renatal consultation are an indicator of effectiveness of methods of primary prevention. The analysis of the repeated cases of treatments will open problems and the hidden opportunities of the effective prenatal consultation for families with SCA1and will help to plan the further direction of researches.

MATERIALS AND METHODS

According to the register of hereditary and congenital diseases of the Medico-genetic center of the Perinatal center of National Medical Center№ 1, 1197 patients stayed on the dispensary registry in group of hereditary diseases with the autosomal dominant inheritance from whom 252 people with a spinocerebellar ataxia type 1 [6].

The research joined over-18 years-old women from the burdened families. Clinical genealogical analysis, prenatal medico-genetic consultation, talking, method of the voluntary informed consent, medical ultrasound of a fetus, invasive prenatal diagnostics by abdominal approachwith ultrasound control and diagnostics DNA methods (DNA purification, PCR, electrophoresis, detection of mutant alleles) were used in the research.

Prenatal diagnostics of diseases with dynamic mutations was carried out in the department of Prenatal Diagnostics of MGC of the NMC PC №1 in 2002 for the first time.

RESULTS AND DISCUSSION

During the last 10 years of the researches of the burdened families with SCA1, 80 treatments to the prenatal medico-genetic consultation were recorded. For thatperiod,there were the repeated casesof treatments of eleven pregnant womenaged from 23 to 32. From the Ust-Aldansky District there were four families, from the Megino-Kangalassky District - two families, from the Amginsky, Abyysky, Namsky, Churapchinsky and Khangalassky Districts – one family from each district.

Seven pregnant women were the presymptomatic carriers of a SCA1 gene, five of which inherited a disease from the father, two women inherited from mother, four pregnant women treated for repeated consultation married to the carriers of a mutant gene.

From seven female carriers of a mutant gene, six were representatives of earlier examined families during work of the international expeditions of 1992-1995 [7,8].

In our opinion, in structure of repeated treatments the important value has the time period which passed from the moment of presymptomatic DNA testing and the first treatment for the prenatal consultation.

According to our observations, from the moment of presymptomatic DNA testing to the first prenatal medico-genetic consultation it is a period of 1 to 3 years averagely. For example, according to a retrospective analysis of the treatments, it turned out that two women from the burdened families treated during the preconceptional period (before pregnancy).

The analysis of the family treatments where the hereditary carriers were husbands showed that two of four men underwent the presymptomatic DNA testing just before the prenatal consultation. However, these families were also earlier surveyed and informed about characters and features of SCA1. Family P., where the carrier is a father, and so two sons are the carriers of a pathological gene, indicates their willingness about healthy posterity birth during the first consultation. Following the results of prenatal diagnostics in these family two children were born without a pathological gene.

Thus, the total number of treatments for eleven women are 33 cases of pregnancy. Gestational age grouping of primary treatments looks in a certain way: in term up to 10 weeks of pregnancy – 6 cases, from 10 to 12 weeks of pregnancy – 11 cases, from 12 weeks and above - 16 cases among which gestational

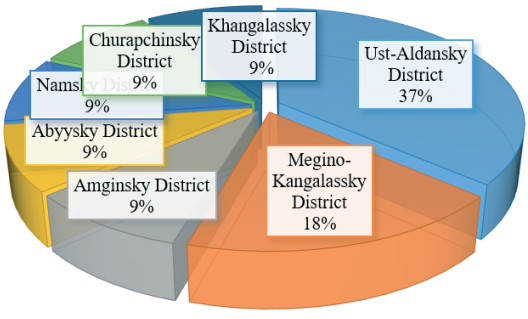

Fig. 1. Districts repeated casesgrouping scheme

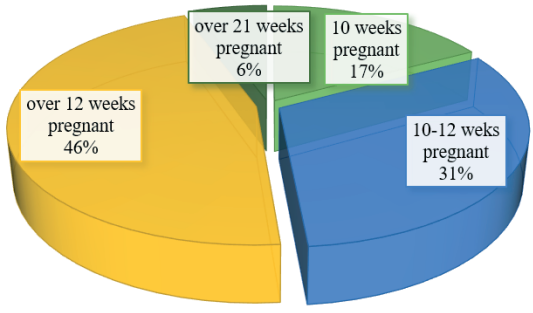

Fig. 3. Gestational age while primary treatment grouping scheme

age over 21 weeks is only 2 cases. Small amount of treatment cases of late pregnancy suggests about preliminary readiness and the conscious choice of treatment period for the prenatal help in caseof the disease.

From 33 cases, in eight episodes not-developing pregnancy was observed (up to 9 weeks of pregnancy at the time of the treatment).

Only 25 from 33 treatments to the prenatal consultation are carried outthe prenatal DNA testing. According to the gestational ages of the patients, a following distribution was observed: up to 12 weeks of pregnancy inclusively – 19 cases, over 12 weeks of pregnancy - 6 cases, among which there was 1 case of carrying out the invasive diagnostics in the gestational age of 25.

Following the results of prenatal testing with the negative DNA test result, 11 pregnant women are referred to pregnancy prolongation. At the same time in two cases with the positive DNA test result the family made the decision of pregnancy continuation. In 12 episodes with the positive DNA test result, the family made a decision to interrupt pregnancy and only three of them was in gestational age from 20 to 25.

Four families have four treatment cases for prenatal DNA testing, three families of whom were described and registered in results of the first international expeditions on studying of the Viliuisk encephalomyelitis and SCA1 in 1992-1995 when probands of our research were at the age of 10-14 years [7,8].

It is possible to assume that the international field researches of SCA1 changed views of a disease from parents of probands that subsequently affected the active and purposeful reproductive behavior of their descendants as since the early childhood there was an opinion about the possibility of anopen discussion and an active intervention in process of inheritance of SCA1. In one of such families having two heterosexual children, a daughter-in-law sought for the medico-genetic help and took the prenatal test four times; subsequently a sister of her husband (sister-in-law), also the carrier of a mutant gene, decided to do the prenatal DNA testing.

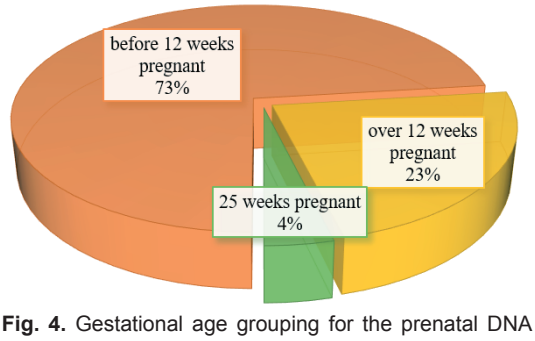

Fig. 4. Gestational age grouping for the prenatal DNA testing

CONCLUSIONS

Preliminary awareness of a family generally and, in particular, young representatives of the burdened families, promotes the early treatment for the preconception land prenatal consultation.

The conducting of the presymptomatic DNA testing to 1-3 years before pregnancy for the women from the burdened families promotes the active treatment to the prenatal consultation.

The repeated cases of the burdened families treatments to the prenatal medico-genetic consultation is an indicator of trust to prenatal diagnostics as the way of achievement of the healthy posterity birth and also efficiency of the prenatal genetic consultation in general.

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Information about the authors:
1. Yakutsk, Republic Sakha (Yakutia), Russia:
2. Sidorova Oksana Gavrilevna -research assistant, department of molecular genetics of YSC CMP, okssi66@mail.ru;
3. Kononova Sardana Kononovna – PhD, senior researcher, department of molecular genetics of YSC CMP, konsard@rambler.ru;
4. Platonov Fedor Alekseevich- MD, Director of the Institute of Health "North-Eastern Federal University named after M.K. Ammosov ", platonovy@mail.ru;
5. Barashkov Nikolai Alekseevich – PhD, Head. of Lab, YSC CMP;
6. Fedorova Sardana Arkadevna – MD, Head of the Laboratory of molecular biology "North-Eastern Federal University named after M.K. Ammosov ", sardaanafedorova@mail.ru.
7. Khusnutdinova Elza Kamilevna, MD, Director of the Institute of Biochemistry and Genetics elzakh@rambler.ru, Ufa, Bashkortostan;
8. Izhevskaya Vera Leonidovna – MD, Deputy Director on scientific work, Research Centre for Medical Genetics, izhevskaya@med-gen.ru, Moscow, Russia.

S.A. Fedorova

ORIGIN OF THE YAKUTS: MOLECULAR-GENETIC RECONSTRUCTIONS IN COMPARISON WITH THE HYPOTHESES OF HISTORIANS

ABSTRACT
This review presents the results of studies of the genetic history of the Yakut (Sakha) people conducted by researchers of the Yakut Scientific Centre of Complex Medical Problems and M. K. Ammosov North-Eastern Federal University (Yakutsk, Russia) in collaboration with the researchers of the Estonian Biocentre (Tartu, Estonia) and the Institute of Biochemistry and Genetics (Ufa Scientific Centre of RAS, Ufa, Russia), over the period 2002-2016. The obtained results are compared and contrasted with the reconstructions proposed by other groups of geneticists and with historical and archaeological hypotheses on the ethnogenesis of the Yakut (Sakha) people.
Keywords: Yakut (Sakha) people, genes, ethnogenesis, mitochondrial DNA, Y-chromosome.

INTRODUCTION

It is generally believed that the formation of the Yakut (Sakha) ethnic group in the territory of Yakutia occurred as a result of the gradual mixing of Turkic-speaking cattle-breeding tribes migrated from the south to the middle Lena River with local tribes over a long period of time. During the Soviet period, archaeological surveys were conducted in the Baikal region and Yakutia to study the earliest stages of the history of the Yakut (Sakha) people. Most modern scholars see the relation of the Yakuts to the Kurumchi culture of the Baikal region (6th to 10th centuries) [7,16,23,29]. Traditionally, the tribes of the Baikal Kurykans are considered to be the immediate ancestors of the Yakuts; apparently, they represented a union of three Turkic tribes, since they are referred to as *Uch-Kurykan* – 'three kurykans' in ancient sources [23]. Kurykans as a separate ethnic group appeared as a result of the assimilation of the aboriginal population and some Mongol-speaking groups by Turkic-speaking Teles tribes who moved to the Baikal region in the 5th-6th centuries [7].

Historians and archaeologists differ significantly in their opinions on the time when the ancestors of the Yakut people migrated to the north. Outstanding Yakut ethnographer G.V. Ksenofontov believed that the Yakuts are an ethnic group of mixed origin, which included three waves of Turkic-speaking immigrants. In his opinion, the first Yakuts began settling in the Vilyui River basin at the end of the 1st century AD; the second wave of the Yakuts migrated to the middle Lena and Vilyui from the Baikal region in the 6th-7th centuries AD; and finally, the last stage of the Yakut settlement occurred in the 11th-12th centuries, triggered by the strengthening of Mongol tribes and the complete displacement of the Yakuts' ancestors from the original place of living [20]. A.P. Okladnikov assumed two "decisive stages" in the settlement of the Yakuts' ancestors in the north. The first, in his opinion, began in the early Iron Age and ended in the 10th-11th centuries; the second stage dates back to the 15th-16th centuries [23]. According to archaeologist I.V. Konstantinov, the migration of the Yakuts' ancestors from the Baikal region occurred in the 15th century, as a compact group, which represented a fully developed ethnic community [19]. More recent researchers believe that the mass migration of the Yakuts' ancestors to the north occurred at the beginning of the 2nd millennium AD and is characterized by the appearance of the Small Houses Culture in Yakutia in the 13th century, which was later replaced by the Kulun-Atakh cattle-breeding culture. [16] On the other hand, archaeological findings (specific arrowheads, details of the bow, armor plates, cult pendant amulets, bull bones) and the appearance of runic inscriptions on the Lena petroglyphs testify