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THE ISSUE OF THE FATE OF A FOETUS WITH A MUTATION AFTER A PRENATAL DIAGNOSIS OF SPINOCEREBELLAR ATAXIA TYPE I IN COMPARISON WITH MYOTONIC DYSTROPHY IN THE SAKHA REPUBLIC (YAKUTIA)

ABSTRACT

We discuss one of the issues of prenatal diagnostics – the bioethical dilemma of the fate of a foetus with a mutation. We believe that prior to the onset of the disease, the individuals-carriers of SCA1 gene mutation cannot be called diseased, as they are completely healthy in their physical and intellectual development.

The phenomenon of DM anticipation depends heavily on inheritance from diseased mothers and increases the risk of birth of an almost completely unviable baby with a severe congenital DM. An ethical dilemma arises: «Should we classify spinocerebellar ataxia type 1 as a ‘less serious’ genetic disease for prenatal diagnostics, and myotonic dystrophy as a more serious disease for prenatal diagnostics?» This is a very complex issue and requires discussion not only among the specialists, but also lawyers, psychologists and the general population of the republic.

Keywords: bioethical issues, prenatal diagnostics, spinocerebellar ataxia, myotonic dystrophy, Sakha Republic (Yakutia).

INTRODUCTION

Prenatal diagnosis (PD) of hereditary diseases is a complex set of modern diagnostic procedures performed at various stages of prenatal development with an aim of identifying possible pathologies that a foetus might have. In Russia, PD saw widespread use only recently, starting with PD of chromosome pathologies using non-invasive methods of ultrasound detection with biochemical markers. At present, PD can identify almost all single-gene disorders with determinable causes: the known mutations of damaged genes. Methods and capabilities of genetic PD are constantly improving, as listed by V. Baranov (2015), who identifies five main modern approaches to PD:

1. molecular diagnosis of chromosomal disorders;
2. microdeletion analysis using microchips (comparative genomic hybridisation – array CGH);
3. pre-implantation diagnosis of chromosomal and genetic disorders;
4. non-invasive PD (NIPD) of chromosomal and genetic disorders by screening foetal DNA obtained from maternal blood (new generation sequencing – NGS);
5. preventive genetic testing (PGT) to identify mutations in married couples when planning a pregnancy [1].

Nevertheless, despite all the advantages of PD as an effective means of preventing hereditary pathologies, with the real possibility of reducing the so-called “evolutionary baggage” of population, there is “another side of the coin” to it: complex bioethical issues that accompany the reproductive decision of a couple – prenatal medical-genetic consulting, obtaining informed consent, making a difficult decision about the fate of an unborn child.

Bioethics researchers P. Tischenko and B. Yudin (2006) emphasize the principal bioethical issues of using genetic technologies:

- involvement of patient’s relatives in the process of genetic testing that undoubtedly raises the question of information confidentiality;
- the gap between the theoretical possibility of diagnosing any presently known hereditary disease and the ability to effectively treat it;
- the use of obtained information for carrying out future prenatal diagnosis in a family to prevent the risk of birthing a second sick child;
- probabilistic nature of the appearance of certain genetic disorders in the subject [10].

S. Deryabina (2015), researching the specifics of medical-genetic consulting in the field of neonatal screening, asks: “Do the parents have the right to know about the genetic state of a child with a late-onset disease? Knowledge is not always beneficial to the one who strives for it. All people are different, and for some, forewarned is really forearmed, while the others buckle under the pressure of impending and inevitable fate, forever losing the ability to enjoy life today and tomorrow, not considering the possibilities of the future” [3].

It seems very natural for a family burdened with a hereditary disease to want to have a healthy child; however, the most pressing bioethical issues arise when deciding whether to keep or to abort a foetus diagnosed with a gene mutation that is responsible for the development of the disease. Let us consider the two most widespread hereditary diseases in the Sakha population, for which PD is possible or is already being practiced.

Materials and methods

Genealogical method of research, collection of medical-social data using genetic maps of patients. Molecular-genetic research methods. Sociological research methods (sociological monitoring, interviews).

The article uses data from the republican genetic registry of hereditary and congenital diseases. According to the genetic registry, 252 patients with spinocerebellar ataxia type 1 diagnosis

and 185 patients with Rossolimo-Curschmann-Batten-Steinert myotonic dystrophy diagnosis were registered in medical-genetic consultation [8].

Results and Discussion

In the year 2000, molecular-genetic methods of research and prenatal diagnosis of five widespread single-gene disorders were introduced for the first time to the medical practice of the Sakha Republic (Yakutia) [4]. From 2000 to 2018 the number of hereditary diseases available for DNA diagnosis increased to 30 conditions [6]. It seems that for each disease it would be possible to conduct PD during the early stages of pregnancy and to prevent the birth of a sick child, however, there are numerous bioethical concerns about the appropriateness of PD in each specific case of prenatal assistance.

Spinocerebellar ataxia type 1 (SCA1)

The disease is characterised by a late onset. On average, the disease develops at the age of 35, although there are significant outliers depending on the number of CAG repeats in mutated *SCA1* gene. There are cases when the disease developed at the age of 26 and the age of 55. Clinical signs of SCA1 are characterised by extreme polymorphism, cerebellar syndrome with pyramidal signs. The disease progresses in 5 clinical stages, defined by the severity of motor and speech dysfunctions. The severity of the disease in the later stages is defined by the development of bulbar paralysis [7].

We believe that prior to the actual onset of the disease, the individuals-carriers of SCA1 gene mutation cannot be called diseased, as they are completely healthy in their physical and intellectual development. Among the carriers of SCA1 gene mutation there were and there are many well-known sportsmen, political and public figures, scientists etc. Let us think for a moment: by suggesting a termination of pregnancy to parents of carriers of SCA1 disease, we are, in essence, suggesting to get rid of a productive member of society. The main reasons why termination of pregnancy can be suggested to parents are the incurable nature of the disease and the suffering of the individual in the future. On the other hand, many laboratories are working on finding a treatment for neurodegenerative diseases and may one day be successful.

In our experience, there were several cases when pregnant women refused to terminate pregnancy when the foetus had SCA1 mutation. Their difficult and informed choice was accepted, just like the choice of the women who decided to terminate pregnancy after receiving positive results of DNA testing. We have also observed that about half of all the women who came to us for SCA1 PD did not return for the actual PD procedure after attending the first prenatal genetic consulting session. This fact shows the moral and psychological difficulty of the challenge to decide the fate of a foetus. There is another example when a woman carrier of SCA1 told us about her apprehension of the disease and expressed her wish to give birth to a child, preferably a girl (even if she inherits the mutation), so that the child could look after her in the future.

Let us look at international documents on the issue: “if the parents are set against the abortion, the test data will not benefit them nor their child, but can cause extreme harm to the child from stigmatisation in the family or society. If, after consultation, the parents still refuse the possibility of an abortion, it would be more ethical to abandon the prenatal test. In this case, testing a foetus for a disease with late onset becomes similar to testing a child, the procedure that WHO experts recommend postponing until the child reaches the legal age” [13, 14].

Myotonic dystrophy (DM)

It is a hereditary neuromuscular disease, characterised by multisystem involvement with a large diversity of clinical symptoms, principal of which are myotonia, myopathy, cataract, cardiomyopathy, endocrine disorders, and, in severe cases, psychoneurological disorders and lowered intelligence. DM mutations, like in SCA1, are considered dynamic and are expressed in the expansion of CTG repeats [2].

Myotonic dystrophy manifests in general by asthenia of a patient and the relative lowering of his or her intellect, due to which it can be difficult for a pregnant woman with DM to make an informed decision about undergoing PD. Similar cases are described in literature in connection with prenatal genetic consultation of teenage girls. The authors identified differences in methods of communication with teenagers and adult women. Teenagers have difficulties in understanding information relating to the risks to foetus [12]. We have also encountered complex ethical and legal issues relating to prenatal diagnosis of DM, as well as conditions that could lead to violation of patient’s rights. With an official disability, many patients with DM are considered legally competent, i.e. they don’t have official caretakers and thus have the right to make an independent decision about PD and the right to give informed consent. However, in almost all cases, patients with myotonic dystrophy depend greatly on their relatives, they and their children are taken care of by the healthy members of their families. It is not unreasonable that in such cases relatives actively influence the decisions made by DM patients. The principle of confidentiality also loses all significance within such a family. We have observed that a considerable number of women who came to us for DM PD were representatives of two large families of R and D. A key role in this was played by the most active members of these families, mostly women, who informed all their relatives of the possibilities of prenatal diagnosis.

Unlike SCA1, DM has a type that causes birth defects. The phenomenon of DM anticipation depends heavily on inheritance from diseased mothers and increases the risk of birth of an almost completely unviable baby with a severe congenital DM, and, at the same time, the mother is also at risk due to the weakness of labour [9].

Conclusion

Doctors and bioethics specialists are in discussions about the seriousness of indications for carrying out PD for hereditary diseases. There is an opinion that the period of full healthy life before the development of late-onset diseases such as SCA1 makes these diseases “less serious” for PD. Overall, the doctors agree that the seriousness of indications for carrying out PD depends on the magnitude of risks, early onset and severity of symptoms [5,11]. Therefore, it is clear in this context that DM is a more serious indication for PD and that families should be strongly recommended to undergo it.

It is not possible to fully discuss the complexity of this issue in a small article. Each case of prenatal diagnosis that identified a mutation in a foetus is a psychological stress and a moral dilemma for a pregnant woman and her family. Prenatal medical-genetic consultation should be carried out in accordance with international bioethics principles:

- voluntary nature of prenatal diagnosis;
- completely and fully informing families about all the possible consequences;
- assistance for a family in making a reproductive decision;
- the choice of families regarding a pregnancy with an affected child should be respected and protected by the respective country’s legislation.

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