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PRECONDITIONS FOR THE DEVELOPMENT OF NEUROETHICS IN CLINICAL PRACTICE OF YAKUTIA

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In recent decades, a new interdisciplinary direction of research in the field of neurobiology has been formed – neuroethics. The aim of the article is to discuss the possibility of introducing neuroethics into clinical practice, since complex methods that differ from traditional ones are used for examination, treatment, rehabilitation and prevention of neuropathology. At the stages of treatment, rehabilitation and prevention of neurodegenerative diseases, ethical questions and dilemmas arise that force health professionals to make decisions, reflecting on the moral problems that arise in the process.

Keywords: bioethics, neuroethics, neuropathology, neurodegenerative diseases, Republic of Sakha (Yakutia)

Introduction. *Bioethical research in Yakutia.* The use of genomic technologies in the clinical practice of medical and genetic consultation of the Republican Hospital No. 1 - National Center of Medicine (MGC RB No. 1-NCM) was several years ahead of scientific molecular genetic research, in particular, the genetic study of the populations of the Republic of Sakha (Yakutia) and the genomic analysis of certain hereditary diseases common among indigenous people. The introduction of molecular methods to the MGC was associated with methodological and ethical issues of DNA diagnostics as a routine analysis to detect gene mutations in patients seeking medical and genetic care. The first were patients with neurodegenerative hereditary diseases (NDD), in particular with spinocerebellar ataxia type 1 (SCA1), which occurs in Yakutia with a frequency of 46 : 100000 [3] and with myotonic dystrophy (MD) - 21.3:100000 [1]. Until the year 2000, the MGC of Yakutia did not have its own molecular genetic laboratory, so it had no experience of conducting genetic analyses and no knowledge of principles of medical genetic counseling related to DNA testing of hereditary diseases.

Moral issues related to the autonomy of the individual, confidentiality, accessibility of genetic information to the patient were discussed by us collegially, decisions were made in accordance with international standards of bioethical regulation of medical genetic counseling and genetic research involving humans.

We needed to establish algorithms for the relationship between the doctor and the patient when referring for DNA testing, taking into account the ethnospecific and psychological aspects of genetic counseling; provide the patient with a voluntary informed consent (VIC) form for presymptomatic DNA testing, develop a procedure for medical personnel when referring a patient for prenatal diagnosis of monogenic diseases diagnosed at the MGC RB No.1-NCM.

Bioethical research in Yakutia was conducted in parallel with the introduction of molecular genetic methods for diagnosing hereditary diseases into clinical practice, as a result of which ethical rules and principles were adopted, in accordance with our local working conditions [2,4].

Prerequisites for the development of neuroethics based on bioethical research in Yakutia. In recent decades, a new interdisciplinary direction of research in the field of neurobiology has been formed – neuroethics [20,23,32]. The most intensively innovative neurotechnologies are developed at the National Institutes of Health (USA), also its own professional community was founded there (International Neuroethics Society), which deals with ethical and social contradictions and professional problems of specialists in the field of neurology, including neuroscience [11, 13, 16, 32].

It is important for neurologists to develop familiarity with the analysis of the ethical problems of neurobiological research and the regulatory challenges arising from experience with patients with neurological diseases and caregivers to ensure quality medical practice [11,32].

This article discusses the main issues of neuroethics and the possibility of introducing neuroethics into the clinical practice of Yakutia.

The activity of the Center for Neurodegenerative Diseases in the clinic of the Yakut Science Center of Complex Medical Problems (CNDD YSC CMP) has prerequisites for the development of neuroethics, since:

- neuroscience is one of the main priorities of the YSC CMP;
- a feature of the scientific activity of the clinic is the study of a certain contingent of patients with neuropathology, including those with rare and unexplored forms of the disease;
- neurodegenerative diseases common in Yakutia are the most important medical and social problem of our time;

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- for the examination, treatment, rehabilitation and prevention of neuropathology, complex methods are used that differ from traditional ones;

- at the stages of treatment, rehabilitation and prevention of neurodegenerative diseases, ethical questions and dilemmas arise that force health professionals to make decisions, reflecting on the moral problems that arise in the process.

Problems of neuroethics in clinical practice. *Joint decision-making.* In patient-centered care, collaborative decision-making is seen as the preferred form of medical decision-making [24,25]. It is a partnership that allows clinicians and patients to make decisions related to health and care, treatment, management or support, based on the best available clinical data and the patient's own values and preferences [31].

The most important category of this issue is the communication process, which consists of five stages: separation of goals, exchange of information, discussion, mutual agreement and follow-up actions. Depending on the conditions, treatment, care planning or rehabilitation options are available. Individual desires and expectations for treatment / care are taken into account, including information needs, own opinions, preferences / values containing what is most important for the patient. Clinicians supplement the recommendations by sharing their clinical experience with examples from previous experience related to the disease and its treatment [5]. For a deeper understanding, healthcare professionals give patients and their relatives enough time to dwell on this in more detail and even collect additional information at home without any stress or pressure [26].

The patient's representatives, the patient himself, and the physician discuss and ultimately reach a consensus on diagnostic decisions and further treatment plans [27]. They make decisions together and jointly agree on them [6,7].

In clinics related to research activities, there is a need to include persons with cognitive impairments in the research project, for which VIC registration is required. In this regard, prerequisites may arise for various kinds of violations of the patient's rights. The patient belongs to a vulnerable group of research participants, these persons are often incapacitated and unable to understand a large amount of complex information and are unable to express their consent. In cases of senile dementia, cognitive impairment, Alzheimer's disease, etc., it is possible to involve close relatives or caregivers to collect VIC [17]. Ethical commissions and committees of various levels play an important role in the ethical examination of scientific projects and the protection of patients' rights.

Patients with NDD can have cognitive and mental impairments of varying degrees, so the problem of VIC will be as important for them. Physicians, neuroscientists will need to learn to disclose sufficient information in an accessible form and receive confirmation from patients of the ability to voluntarily choose between consent or other options [31,22,30].

Difficulties in disclosing family history. Discussing family history is a vulnerable experience for some patients with hereditary, neurological, mental illnesses. There may be scenarios of limited awareness of their family members' health history or a patient's lack of interest in discussing family history [19,21].

But this should not be an obstacle to patients' participation in the studies. It is possible to interest the patient in the joint recreation of their family tree, as an opportunity to talk unpretentiously about family history and help to recognize the generations affected by the disease.

Respectful and inclusive attitude to the patient expands his/her decision-making opportunities and builds a relationship in the field of health care, in which the patient and the neurologist work together as a team to ensure maximum efficiency of medical care [33].

In addition, for example, genetic testing in clinical neurology may accidentally reveal unforeseen genetic information completely unrelated to the study, which has potential adverse consequences for both the patient and the family [9].

Genetic testing can also affect family members by inadvertently identifying mutations in asymptomatic at-risk individuals who previously chose to avoid this knowledge (or did not consent to testing) and who may be subject to psychological harm or discrimination. Similarly, genetic testing can affect family relationships by accidentally revealing incorrectly established paternity. The risk of accidental genetic findings may be particularly important for paediatric research participants and others with disabilities. Such participants may find that their future lives have changed significantly or are limited as a result of decisions by parents or guardians to direct them to genetic testing [9].

Use of pharmaceuticals that affect cognitive and behavioral functions. The prospect of developing pharmaceuticals designed specifically to improve cognitive, affective and motivational processes has raised a number of ethical questions. They raise serious concerns, since it is possible that these pharmaceuticals can be used to improve human health in unacceptable ways, and they can also contradict the very nature of man, because they can have serious side effects (Table).

Drugs used for treatment and their side effects [18]

Drug	Usage	Possible effect
Glucocorticoid	Relief of asthma symptoms, reduction of adrenal insufficiency, autoimmune conditions	Improved concentration, psychosis, memory decline, mood changes, memory improvement, especially for emotionally stimulating events
L-dopa	Treatment of PD	Excitement, confusion, psychosis, agitation and anxiety
Lithium	Treatment of mental illness, bipolar disorder	Possible increase in motivation due to prevention of signs of depression, reduction of paranoia, pomposity and risk appetite
Methylphenidate	Treatment of ADHD, hyperactivity, narcolepsy	Irritability, psychosis, signs of increased attention, confusion, improvement of working memory
Modafinil	Treatment of sleep disorders, improvement of cognitive functions in narcolepsy	Signs of aggression or anxiety, increased vigilance and attention, improved working memory
Pramipexole	Treatment of PD	Pathological gambling, hypersexuality, paraphilias (e.g., pedophilia), compulsive behaviors (e.g., compulsive shopping and dressing up)

Millions of doses of pharmaceuticals affecting cognitive abilities and affects are consumed annually, an empirical and philosophical analysis of their effects is the objective of neuroethics [18].

Pharmaceuticals influence important elements of moral decision-making and human behavior. Some dopamine agonists (pramipexole, etc.) used to treat Parkinson's disease (PD) may be examples of drugs with possible morally important behavioral effects (consequences). Publications discuss cases that these drugs caused gambling addiction and hypersexuality in some people [28,12].

Anxiolytics – drugs used to treat disorders associated with excessive anxiety can also have a morally significant effect, given that anxiety can cloud decision-making, including moral [10].

Thus, the assessment of the effect of pharmaceuticals on cognitive and behavioral functions requires not only further scientific research, but also important moral conclusions.

Application of advanced neurotechnologies. Several generations ago, it was impossible to imagine such technologies as neuroimaging, brain stimulation, neural implants, brain structures and areas, mobile technologies, improvement of cognitive functions, brain-computer interfaces, robotics, exoskeletons, artificial intelligence, etc. For example, studies of functional MRI gradually raise new ethical problems, as studies of neural models related to decision-making, memory recovery, personality traits, behavior, perception of surrounding stimuli multiply [29]. Various mental states and processes with neuronal activity in certain areas of the brain, once used to decipher mental activity, may find applications unrelated to medicine or biology, a potential abuse aimed at gathering information that is normally prohibited by law [32]. Significant progress has been made in the field of neurobiological research, for example, it has become clear that the results of studying the cells and mechanisms of brain activity in experimental animals and humans differ significantly [8]. A recent publication by Gidon,et al., 2020 in Science investigated the dendrites of pyramidal neurons of layers 2 and 3 (L2/3) of the human cerebral cortex ex vivo in slices of surgically removed human neocortical brain tissue in patients with epilepsy and tumors. For the first time, the subtle mechanisms of dendritic Ca2+ axonal action potentials in human neurons, as well as previously unknown dendrites that are not characteristic of animal neurons, which may be responsible for human mental activity, have been described [14,15]. In "J Clin Invest", Fernández, et al.,2021, published a successful case in implanting an intracortical matrix (consisting of 96 electrodes) into the visual cortex of a 57-year-old woman with complete blindness for a 6-month period. The results allowed the participant to identify some letters and recognize the boundaries of objects [14,15].

Society should be prepared to examine the ethical considerations surrounding neural modifiers on a case-by-case basis and consider the intervention, its purpose, who chooses it, who may benefit from it and who may be harmed. For example, DBS (deep brain stimulation) to improve symptoms of a mental disorder such as depression can be ethical if it is proven to be safe and effective, and if it is freely chosen by a fully informed adult. However, DBS would be ethically problematic if an adult were coerced into taking it.

Guidelines developed by professional organizations such as neurological associations could be of great help in informing the public and assisting health professionals and other stakeholders in understanding neural modifiers and their potential benefits and risks in different circumstances.

Conclusion. A growing awareness of the ethical implications of neuroscience research in the world has shaped the field that has come to be known as neuroethics.

Neuroethics intersects with biomedical ethics in the sense that neuroethics also deals with the ethical, legal, and social implications of neuroscience findings, as well as the nature of the research itself.

The importance of the properties of the nervous system, the special relationship between the personality and the brain, the influence of human life itself on its neurological functions give rise to more and more novel ethical and philosophical problems.

Neuroscientists can collaborate with neuroethics researchers to advance clinical neuroethics. Neuroethics can also be successfully combined with other specializations in neurology, in particular, synergistic specializations such as neurocritical therapy, cognitive-behavioral neurology, stroke, neurorehabilitation, neurogenetics, global neurology, neurophysiology, and neuropalliative care.

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