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Review

A general overview of ethical issues encountered in rare diseases

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ABSTRACT

Rare diseases are diseases that are seen quite rarely in society with a prevalence of 1/2000. However, this prevalence varies from country to country. These diseases are serious, chronic, and reduce the quality of life and expectation. The lack of sufficient medical and scientific information about them prolongs the diagnosis process. The prolongation of the diagnosis period makes it difficult for the physician to make a diagnosis in the clinic, while the time works to the detriment of the patient. Since their drugs are not profitable drugs, their development has been neglected and they have been defined as orphan drugs. In addition to the difficulty of accessing drugs and the high costs, the difficulty of caring for these diseases brings psychological, social and economic burdens to the person or persons providing care to the patient. Such difficulties bring many ethical problems. In this study, some ethical issues encountered in rare diseases will be discussed.

Keywords: Rare diseases, health ethics accessibility of treatment, social justice

Introduction

Diseases with a prevalence of less than 1 in 2000 are defined as rare diseases (orphan diseases). This rate, which usually affects children and is 80% genetic, can vary from country to country, so the rate of occurrence in society varies. For example, the rate of these diseases in France is 3 million, while it is around 25-30 million in Europe overall. These diseases, which affect multiple systems, manifest themselves with mental and physical disorders that reduce the quality of life. While the rate of occurrence in our country affects 5-8% of the society, 6-8% of the world is affected (1). This means that approximately 5-6.4 million people in our country and 473 million of the world's population suffer from this disease. Since these diseases are rare in societies, the difficulty of diagnosing them is experienced all over the world, and in this context, diagnosis and treatment centers are being opened to increase this awareness, especially in Europe and the United States. In addition, the lack of treatment options and limited access to these treatments increase mortality and morbidity (2). Although rare diseases are rare, they bring with them a lot of problems. The rarity of the disease causes physicians to be inexperienced about these diseases and causes time to be lost in diagnosis, limited or no treatments cause patients to have difficulty accessing treatment, studies on these diseases are still insufficient, especially when they are seen in children, parents who care for the child experience both psychological and economic difficulties, and ethical problems such as stigmatization in society arise (3). In 2018, the United Nations

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published the "Rights of Individuals Living with Rare Diseases Document" regarding the rights of individuals with rare diseases. The document draws attention to the problems of individuals with rare diseases. These are the difficulties in diagnosis due to the lack of a well-organized infrastructure for these diseases, the lack of treatment for some diseases, the difficulty in finding medicine, the difficulty in providing care, and the difficulties these individuals experience in accessing health services. Therefore, many ethical problems arise in the context of human rights (4). These diseases, which reduce the patient's quality of life and life expectancy, also bring some ethical problems in the context of human rights with the difficulties they bring. This study will discuss some ethical issues caused by rare diseases (5).

Difficulty in Diagnosis

Approximately 8000 rare diseases are seen in 1 in 2000 people. The number of people who meet this qualification is approximately 5 million in Turkey (6). Almost all pediatric and some adult cancers meet the definition of rare disease. The fact that clinicians do not have much information about these diseases causes these patients to apply to many health centers for a long time (7). The fact that their prevalence is quite low compared to other diseases, and that there is little participation in research to have more information about them and to develop drugs can leave physicians uninformed on this subject. Even if a physician suspects a rare disease, many tests will need to be performed on the patient, otherwise a wrong diagnosis will lead to wrong treatment and harm to the patient will be on the agenda. In addition, the lack of adequate testing environments in developing countries to make a full diagnosis and the lack of attention paid to these diseases by some governments will make it difficult for individuals with rare diseases (5). For example, diagnosing telomere disorders can be almost impossible for a clinician. It has been reported that rare diseases such as these are not taught in medical schools or are not emphasized much. This may be true for almost all rare diseases. The small number of patients and the fact that they are not taught as a subject in schools or not at all make it difficult for clinicians to diagnose these diseases. However, early diagnosis increases the patient's chance of survival and quality of life. An incorrect and/or delayed diagnosis worsens the prognosis and reduces the patient's chance of survival (1).

Orphan Drugs

Rare diseases are a significant public health problem. The reason why drugs used in rare diseases are called Orphan Drugs is that pharmaceutical companies spend more money on the development and production of these drugs than on their marketing, meaning they do not bring profit. Pharmaceutical companies do not want to develop drugs unless they can make a profit from these drugs because the number of individuals with this type of disease is quite low. Therefore, this situation causes the price of orphan drugs to be high (8). The European Union has used this term for drugs developed for life-threatening and/or chronic diseases that are rare in society and do not bring profit. The reason why these drugs are called orphan is that their production has been neglected (9). Drug development is a very long and costly endeavor. This situation has become more difficult in orphan diseases. The very small number of patients, the wide geographical distribution of patients, the inability to make a complete and timely diagnosis in the clinic and the length of the diagnostic process, and the inability of pharmaceutical companies to make a profit because they will produce a limited number of drugs prevent the production of these drugs. Since it is not known exactly how orphan drugs are priced, they are called "black boxes". Due to their low prevalence and limited demand for drugs, it was impossible to produce these drugs in the United States (US). There were only 10 drugs in the 1970s. To encourage the production of these drugs, the Orphan Drug Act was passed in the US in 1983. This law included the following: 1)

7-year market exclusivity would be given to off-patent drugs used for rare diseases. 2) Credit opportunities would be provided for research and development expenses. 3) Elimination or reduction of procedural fees. 4) Applications for orphan drugs would be submitted to the FDA (Food and Drug Administration) for approval and designation as orphan drugs. 5) Research grants from the National Institutes of Health for drug development. The number of rare drugs increased with this law. However, the high prices of medicines and the problem of access to drugs continue. This is also considered problematic in terms of the principle of justice. In this context, policy makers recommend that more egalitarian laws be made in terms of justice (10). The lack of a globally accepted norm regarding the prevalence of rare diseases also prevents a global consensus. The principle of justice, one of the principles of medical ethics, generally deals with the distribution of health services. In the context of Human Rights, the principle of justice is concerned with all people accessing this service. However, orphan drugs pose an ethical dilemma in this regard. When we look at the texts where the principle of justice is divided into procedural, distributional and social subcategories, procedural justice deals with transparency in decisions taken; distributive justice deals with the fair distribution of limited resources; and social justice deals with treating people with the dignity and respect they deserve. The issue of orphan drugs falls outside these scopes. Therefore, all procedures from the development of orphan drugs to the determination of their prices should include transparency, and access to these drugs is important in terms of both social and distributive justice. In addition, the development of orphan drugs is also approached with a rights-based and egalitarian moral understanding. Since the utilitarian perspective aims at maximum benefit, there are concerns about the exclusion of rare diseases. The rights-based approach aims to meet the legitimate demands of the individual or group based on human rights. In this case, there should be a minimum right to health care for rare diseases (11). Article 35 of the Charter of Fundamental Rights of the European Commission on health care states: "Everyone has the right to access preventive health care and the right to benefit from medical treatment under the conditions determined by national laws and practices. A high level of human health protection shall be ensured in the definition and implementation of all Union policies and activities." (12). Alongside all these ethical discussions, the principle of "non-abandonment" is discussed. This approach is based on social moral obligations and the benevolence that is the basis of professional moral obligation.

Improvement of Databases

It is a necessity to have biobanks where information about patients with rare diseases will be collected. To develop orphan drugs and obtain more advanced information about the disease, patient data needs to be collected in a common database worldwide. However, the small number of patients also causes the patient data to be collected in the database to be small. In addition, patients may be concerned about the confidentiality of their data (13). However, the fact that each country has different laws prevents the collection of patient data in a common database. This practice brings with it many ethical issues regarding informed consent and confidentiality of patient data (14). In 1997, orpha.net, which currently provides services in 8 languages, provides information on clinical symptoms of rare diseases, orphan drugs, laboratory tests, research, and data. A database providing information about patient data, patient organizations, and institutes has been established (15).

Functioning of Ethical Committees

Some authors suggest the establishment of an ethics committee for rare diseases, while others may oppose it. While it is suggested that interdisciplinary ethics committees should be formed by the best experts in medicine, law and ethics, some authors argue that ordinary

individuals should also be included in the committee. However, in addition to all this, the approval of this ethics committee is required for a research and development to be conducted for rare diseases, and some authors have stated that the decision to be made by the committee takes years. Therefore, both the long duration of the research and the long duration of the decision will not be beneficial for the individual with a rare disease (16). Therefore, a systematic study should be conducted on the functioning of ethics committees, and bureaucratic problems should not prolong the process. The existence of an ethics committee ensures that the benefits of the volunteers are provided and prevents them from suffering any possible harm. The research process for rare diseases is both long and the number of patients is low. The fact that ethics approval takes years means a waste of economic resources allocated to research for these chronic, progressive, serious and life-threatening diseases. At the same time, a long wait can cause the death of the patient. In this context, the ethics committee should protect the volunteer's interests, but this situation may harm the volunteer (17). Ethics committees must include a person who is an expert in rare diseases. In addition to granting consent for the research to be conducted, they should control any activity that will put the participant at risk. Since the number of individuals with rare diseases is very small, these studies are successful with participants from other countries. However, the biggest problem in this situation is that these studies are conducted in developed countries and patients from developing countries are also needed. Developing countries may not have an ethics committee or ethical standards may not be followed strongly. In such a case, since international cooperation is needed in the field of ethics, there is a need for training of experts in the field of ethics and rare diseases in developing countries. Ethics committees should not only approve orphan drug research, but also determine new ethical rules and follow them (14).

Patient-Physician Relationship

Physicians will probably have a different relationship with individuals with rare diseases than the classical patient-physician relationship. Since the physician is knowledgeable about the disease and treatment, they may have a paternalistic attitude that is not considered ethically appropriate. However, the situation seems a bit different in rare diseases. While the physician is facing a patient who is an expert on the disease, he may not have any knowledge about the disease. Therefore, the physician should listen seriously to the patient who describes the symptoms of the disease in the clinic and evaluate every detail well. Rather than increasing the patient's participation in the treatment process, he can keep control of the treatment process (18).

Genetic Screening

While genetic screening performed on embryos, fetuses, newborns and adults has many benefits, it may also pose a risk of causing some eugenic approaches. In countries where health insurance is not guaranteed by the state, many problems can be encountered, ranging from insurance companies to the economic interests of the companies that work. Genetic screening on newborns can help with possible treatments for a rare disease that will be discovered, increasing the quality of life with early diagnosis and positively affecting prognosis, the risk of recurrence of these diseases in the future and helping individuals combat this risk, and taking precautions. There are discussions about prenatal tests, as the tests are 98% accurate, with a 1-2% risk of giving incorrect results and causing abortion of a healthy fetus. Preimplantation tests are performed by testing the embryo formed by in vitro fertilization (IVF) before pregnancy. If the embryo carries a genetic disease, pregnancy is prevented in advance. However, there are ideas that destroying the embryo, this structure that has the potential for life, could be the same as killing a person. It is not ethically appropriate

to expand preimplantation diagnosis to change the child's characteristics such as intelligence, gender, eye, hair, and skin color (5).

Effects on Families

Rare diseases are difficult to diagnose due to the lack of scientific data and prevalence, and they usually affect children. The long-lasting diagnosis process, the need to visit many laboratories and doctors negatively affect families psychologically. The serious symptoms of the disease, the painful treatments applied after the diagnosis, and in addition to all these, parents isolating themselves from social life due to their children's illness have devastating effects on parents psychologically. In addition to all these, the lack of scientific information and definitive treatments, difficulty in accessing orphan drugs, the unknown, the parent's inability to obtain clear information from the doctor about the disease, and the unknown emotionally weaken the parent who provides care for the child. The expenses incurred during the diagnosis process, the need for technological devices to provide home care, the mother quitting her job to provide care, the need for a professional for home care, being dependent on abroad to access orphan drugs, and the parent's absenteeism from work are all directly and directly negative economic effects. The process of providing care for a rare disease that has serious physical effects on the caregiver or parent also has negative physical effects on the caregiver. In summary, rare diseases impose psycho-social, physical and economic burdens on the caregiver (19).

Conclusion

Rare diseases are difficult to diagnose, have no definitive treatment and are a public health problem that brings with it a wide range of ethical issues. They are a public health problem and are also abnormal diseases that clinicians encounter. Lack of medical and scientific knowledge makes it difficult for physicians to diagnose these diseases in the clinic. Including more information about rare diseases in the curriculum of medical schools and providing physicians with training about these diseases at certain periods will increase the clinician's awareness of these diseases, prevent the diagnosis process from being prolonged and prevent harm to the patient. In this context, early diagnosis will increase the patient's quality of life and life expectancy. The emotional fatigue that the parent is experiencing should be evaluated by the physician in the clinic with empathy and it is ethically appropriate to keep the communication dynamic. International cooperation and incentives are definitely needed for the development of orphan drugs. For this, the necessary legal regulations of countries to increase the data in the database are again dependent on this international cooperation. It is essential to establish interdisciplinary ethics committees in countries, including professionals who are experts in their fields, with the primary aim of protecting the welfare of volunteers in research.

Author contribution

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Conflict of interest

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