Ethical Issues Encountered within the Context of an Adrenoleukodystrophy Case

Bir Adrenolökodistrofi Vakası Bağlamında Karşılaşılan Etik Sorunlar

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ABSTRACT

Adrenoleukodystrophy (ALD) is a disorder of peroxisomal fatty acid beta oxidation which results in the accumulation of very-long chain fatty acids in tissues throughout the body. The most severely affected tissues are the myelin in the central nervous system, the adrenal cortex and the Leydig cells in the testes. Clinically, ALD is a heterogeneous disorder, presenting with several distinct phenotypes, and no clear pattern of genotype-phenotype correlation. As an X-linked disorder, ALD presents most commonly in males, however approximately 50% of heterozygote females show some symptoms later in life.
In the case presented in this paper, the subject is a 19-year-old woman who applied to the genetics polyclinic. Her grandmother, mother and two siblings have ALD. She wonders and is concerned about her status as a carrier. Her parents do not want their daughter to take a diagnostic test and the sick siblings in in the family are hidden from the person to whom she will get married. The patient applied to the genetic outpatient clinic without the knowledge of her family, the first tests were performed and the other sick patients at home were also suggested to take a test for the diagnosis to be confirmed. That the patient was prevented from taking a test, that her health information was not shared with the person she will get married to and the patient's wish to have her six-year-old sister/brother, who can not make his/her own decisions take the test, necessitated the discussion of the case ethically.

Key Words: ALD, Medical Ethics, Medical Genetics, Genetic Counseling, Genetics Privacy, Truth Disclosure.

Received: 01.14.2020 **Accepted:** 02.08.2020

ÖZET

Adrenolökodistrofi (ALD), vücuttaki dokularda çok uzun zincirli yağ asitlerinin birikmesine yol açan peroksizomal yağ asidi beta oksidasyonu bozukluğudur. En ciddi şekilde etkilenen dokular merkezi sinir sistemindeki miyelin, adrenal korteks ve testislerdeki Leydig hücreleridir. Klinik olarak ALD, birkaç farklı fenotip ile ortaya çıkan heterojen bir hastalıktır ve net bir genotip-fenotip korelasyonu örüntüsü yoktur. X'e bağlı bir bozukluk olarak ALD en sık erkeklerde görülmektedir, ancak heterozigot dişilerin yaklaşık % 50'si yaşamın ilerleyen dönemlerinde bazı semptomlar göstermektedir. ALD hastalarının yaklaşık üçte ikisi, en şiddetli form olan çocukluk serebral formu ile karşımıza çıkmaktadır.
Yazımız, Tıbbi Genetik polikliniğine danışmanlık almak için başvurmuş 19 yaşında bir kadın hakkındadır. Öyküsünde anneannesi, annesi ve iki kardeşinde ALD mevcuttur. Kendisinin taşıyıcı olma durumunu merak etmekte ve bu konuda endişelenmektedir. Ayrıca altı ay sonra evlenecektir. Ailesi, kızlarının tanı testi yaptırmasını istememekte ve evleneceği kişiden ailedeki hasta kardeşler gizlenmektedir. Hasta, ailesinden gizli genetik polikliniğine başvurmuş, ilk testleri yapılmış, tanının doğrulanması açısından evde bulunan diğer hasta kardeşlere de test önerilmiştir. Hastanın test yaptırmasının engellenmesi, evleneceği kişi ile sağlık bilgilerini paylaşmasına izin verilmemesi ve özerk olmayan altı yaşındaki kardeşe anne ve babadan gizli test yaptırmak istenmesi vakanın etik açıdan tartışılmasını gerektirmektedir.

Anahtar Sözcükler: ALD, Tıbbi Etik, Tıbbi Genetik, Genetik Danışmanlık, Genetik Gizlilik, Gerçeği Açıklama.

Geliş Tarihi: 14.01.2020 **Kabul Tarihi:** 08.02.2020

"We used to think our fate was in our stars. Now we know, in large measure, our fate is in our genes" (J. Watson, quoted in Time Magazine, March 20, 1989).

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doi:http://dx.doi.org/10.12996/gmj.2020.59

INTRODUCTION

Adrenoleukodystrophy (ALD) is an inherited metabolic storage disorder (1). An inherited disorder means that the disease is caused by a faulty gene passed on from parent(s) to children. Genes are instructions that tell the body how to make all the different substances the body needs to work properly. So the affected gene in ALD prevents the body from being able to metabolize certain fatty acids. This disorder consequence the lack of peroxisomal metabolism biochemically, and characterized by the accumulation of very long chain fatty acids (VLCFA) in tissues and biological fluids (2). ALD is a recessive X-linked disorder (X-ALD) associated with marked phenotypic variability. All patients have mutations in the ABCD1 gene and accumulate very long chain fatty acids in all tissues. All male X-ALD patients develop adrenocortical insufficiency in childhood and progressive myelopathy and peripheral neuropathy in adulthood. Female patients also develop progressive myelopathy and peripheral neuropathy, but generally at a later age than males. Female carriers are commonly thought to be normal or only mildly affected.

Although women carriers are usually considered normal or only very mildly affected, it has, in fact, been observed that at least half of the heterozygous females present neurological manifestations that vary in severity, ranging from mild hyperreflexia and vibratory sense impairment with little or no functional disability, to severe spastic paraparesis where the patient may need a wheelchair (1,2,3). This article aims to examine the potential ethical issues that may arise due to genetic tests used for ALD within the context of a specific case.

A CASE REPORT

Patient History

In this case, 19 years old female patient makes an application with complaints of headache. Her two younger brothers have adrenoleukodystrophy, which has an X-linked recessive inheritance pattern. For this reason, the patient is curious about the risks of being a carrier and genetic diagnosis options.

She is to be married six months later and she is unable talk about the disease of her brothers with her future husband because of family pressure. She has been informed by her doctors that her VLCFA level is high, but her family opposes her wish to have a diagnostic test. For this reason, she wants to be tested in secret from her family. Her pedigree can be seen in the following figure (Figure 1):

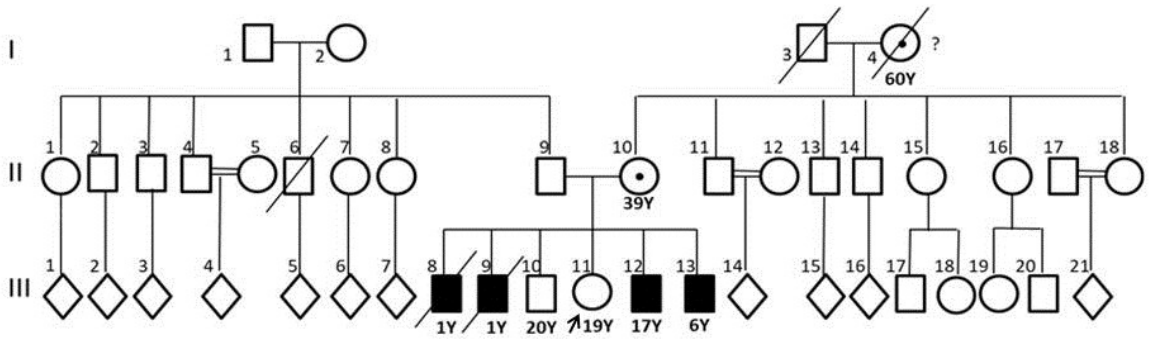

Figure 1. The pedigree of the patient.

Family History

The patient's grandmother (I-4, Figure 1) died at the age of 60. In the last years of her life, she suffered from a gait disturbance, which deteriorated gradually.

The patient's mother (II-10, Figure 1) has the same history of headaches and her VLCFA level is also high. She has had six pregnancies and has four living children. Her first two sons (III-8 and III-9, Figure 1) died before reaching one year of age because of an unknown illness. Our patient (III-11, Figure 1) and her elder brother (III-10, Figure 1) are healthy.

The fifth sibling (III-12, Figure 1) was able to walk at the age of 10, had an accompanying speech disorder and she had gone into a coma at one point. Diagnostic tests showed that her VLCFA level was high and he was diagnosed with ALD. Cortisone treatment, diet and physiotherapy were recommended. His clinical situation started to improve and he is now under follow-up for his disease.

The youngest brother (III-13) has a gait disorder, is on cortisone treatment and receiving physical therapy. He is also diagnosed with Down syndrome and is receiving special education.

The documents about the ALD diagnosis of the patient's brothers are not verified. On the other hand, an ABCD1 gene sequence analysis was planned upon the patient's request. The patient has been informed about the risks of being a carrier for ALD.

Test Results

ABCD1 gene sequence analysis did not reveal a high mutation level. However, because of the high VLCFA level, the diagnosis of ALD cannot be ruled out on the basis of this result alone (3). It is suggested to repeat the tests on the younger brothers. The patient is responsible for taking care of her youngest brother (III-13, Figure 1), who, according to the patient, is not aware of the possibility of the disease. The patient was concerned that her family members would oppose genetic testing and wanted to know whether tests could be done without informing them.

Compliance with Ethical Standards

This study was approved by Baskent University Institutional Review Board (Project no: 18/114).

Human Studies and Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013. Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

The Legal Aspects: Current Laws and Regulations Concerning the Management of Genetic Information

The specific regulation in Turkey addressing the issue is called "Regulation on Genetic Diagnosis Centers" issued in 1998 and amended in 2015. Article 19 of this regulation states the following: "Genetic diagnosis centers may not carry out any procedures without the informed consent of the individual. The results may not be disclosed to third parties without the individual's consent" (4,5).

Turkish Medical Association's "Declaration on Medical Genetics Data", although not legally binding, also addresses the issue. It states the following: "*The informed consent of the individual is essential during the processing, use and storage of genetic data. For the individual who cannot provide her explicit consent, the permission of her legal representative or guardian must be sought. However, genetic tests during the diagnosis and treatment of genetic diseases*

may only be accepted when such tests will provide significant effects for the health and the benefit of the individual".

In addition, the document emphasizes that "*Access of third parties such as employers, insurance companies, education institutions and families to genetic data and information on biological samples should be prevented*". The document also emphasizes that disclosure of the unique nature of genetic data, which may involve not only the individual but also other family members, is significant during the informed consent process (6).

In addition, article 12 of the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, (also known as the Oviedo Convention) ratified by Turkey in 2003 states the following on the issue: "*Tests which are predictive of genetic diseases or which serve either to identify the subject as a carrier of a gene responsible for a disease or to detect a genetic predisposition or susceptibility to a disease may be performed only for health purposes or for scientific research linked to health purposes, and subject to appropriate genetic counselling*" (7).

Ethical Analysis and Discussion

Ethics deals with problems arising from human interactions and actions in general and problems of values in particular. It is the philosophy discipline that deals with the relationship of the person with herself and with others and that clarifies, examines and produces knowledge with regard to issues of moral values (8,9). Ethical issues are value problems that persons encounter when they are making decisions and taking actions within the context of their relations with themselves, with others or with various human conditions (9).

Differences with regard to what is "good" and "right" in ethical arguments leads us to different theories of ethics. Furthermore, ethical theories show us that a particular situation can be interpreted from different angles and they provide us an "explanation of ethical discourse" (10). The mostly used ethical theories are virtue ethics (11), which draws attention to how the subject performing the actual action exhibits his/her properties such courage and benevolence in his/her relations with other individuals and the society, although the characteristics and consequences of the actions are important, deontological ethics (12), based on the assertion that what is to be considered when evaluating actions is not the consequence or outcomes of the action, but the principles or rules that the action concerned is based on and that lead to that action, utilitarian ethics (13), based on the understanding that "the action that provides the highest level of happiness to the greatest number of people with the lowest price is the right action," and the principles ethical theory (14), which is based on principles of providing benefit, not doing any harm, respect for autonomy and justice.

Analysis of ethical issues arising from the applications of genetic technology with a single ethical theory is not an easy task; the situation requires evaluation with various approaches. For instance, while the traditional approach of balancing harms and benefits (the principle of proportionality) can be informing on its own, virtue theory could be useful in delineating the right virtue in case both actions can be morally justified. On the other hand, ethics of care, which emphasizes the responsibilities of individuals towards themselves and towards others in an interrelational context, would emphasize the obligations of individuals towards each other with regard to genetic information. Furthermore, communitarian ethics, which prioritizes the community to which the individual belongs as a whole rather than the individual's autonomy would also be particularly relevant for this case, since it would advocate the integration of the family in the decision-making process and protection of the interests of other family members. Last but not least, case based analysis, which focuses on the specific aspects of the case at hand, would require more emphasis to be placed on the patient's history (14).

Ethical issues involve more than questions that can be resolved by simply answering "yes" or "no"; therefore, they need to be examined in more depth. For this purpose, questions of ethical nature that arise in the context of this case will be noted as below: Is it legally and ethically justifiable for the family to prevent their daughter from demanding genetic testing? Is there a valid moral basis underlying this action? Is the patient's future husband entitled to know anything about the patient's medical history? Does the fact that the patients is responsible for taking care of her 6-year old brother mean that she is entitled to act as a decision-maker on his behalf? Is the 6-year-old brother being used as a means to an end? If genetically testing the 6-year old brother is of vital importance for the patient, would this be enough to justify the use of the test on her brother?

While there exist written guidelines that provide guidance with regard to the use of genetic testing and the management of information obtained through these tests in general, due to the unique aspects of each case, the questions noted above need to be examined and discussed specifically within an ethical framework.

Questions: Is it legally and ethically justifiable for the family to prevent their daughter from demanding genetic testing? Is there a valid moral basis underlying this action?

The request for a genetic test

Humans possess a unique status with regard to their relation with other living things and therefore, they possess certain rights within the context of human-human relationships. While every person has a right to life, right to access to food, right to education, right to bodily integrity etc., these rights are based on the value of the human being (15). Another point that should be emphasized is the ability of the persons to rule or to decide for themselves. This aspect of humans has been addressed within the principle-based framework under the principle of respect for autonomy. Autonomy implies "self-rule that is free from both controlling interference by others and from certain limitations such as inadequate understanding that prevents meaningful choice" (14). According to the principle of respect for autonomy, decisions of autonomous persons should be respected.

In the light of this approach, since the patient in the case we have presented above is a competent adult who can consent to the procedure, the family's refusal of the procedure is not justifiable. The patient has a right to self-determination, and therefore, she is entitled to know about her own medical condition; otherwise, she will not be able to make an informed decision (16) In addition, a competent adult's right to consent to or refuse medical interventions is recognized in Turkey's laws and regulations. Therefore, the family's action is incompatible with the principle of autonomy and has no legal basis.

On the other hand, while this particular action of the family can be seen as unjustified, the possible reasons underlying this decision should be examined. It is understood that although two of the siblings have ALD, their diagnosis has not been documented formally. Furthermore, the patient is hiding the medical conditions of her brothers from her future husband. These particular facts of the case suggest that the family is trying to act as if the disease does not exist or is trying to prevent other people from finding out about this condition. Therefore, it appears that the family is worried about potential stigmatization and discrimination and/or assumes that informing other people about the situation will have psychological consequences which may be potentially harmful.

Genetic tests provide powerful information with regard to future. The nature of this information is not transitory, it is permanent. Sometimes people may imagine the "worst case scenario" when they think about genetic information. For this reason, it should be kept in mind that genetic information may cause anxiety and psychological distress on the individual and may psychosocial impacts in addition to the biological status. Furthermore, the potential of genetic information to cause discrimination at the individual and community level is one of the most frequently voiced concerns about genetic information (16,17). For this reason, it is natural for families to try to protect their privacy by limiting access to genetic information.

For this reason, the family's refusal of genetic testing and can be considered as an attempt to maintain their privacy to provide protection from psycho-social impacts of genetic information. However, while this action may be justified for third persons, we think it is unacceptable in the case of the patient, since it will clearly be a violation of her right to self-determination.

Question: Is the patient's future husband entitled to know anything about the patient's medical history?

Disclosure of Genetic Information to Third Parties

Another questions that needs to be answered on the basis of the specific aspects of the case involves the right of the patient's potential husband to genetic information about the patient.

This question will be examined in the context of reporting the results of genetic tests to third persons who can be potentially affected by the genetic information, as detailed below.

When a person confides information to someone else, there is explicit or implicit assurance that the information will be kept confidential. Information of this nature involves the privacy of the person confiding the information and is based on the trust felt towards the other party. Reporting this information to a third party is not compatible with medical confidentiality, which is a time-honored and significant professional obligation and is therefore considered to be unethical. Medical confidentiality is considered to be rule of categorical nature in medicine (14).

Since genetic information has a pedigree and may be associated with more than one person, the unconditional nature of the duty to maintain medical confidentiality may be subject to a more flexible interpretation. We concur with the recommendation of the Institute of Medicine Committee on Assessing Genetic Risks that "confidentiality be breached and relatives informed about genetic risks only when *(i) attempts to elicit voluntary disclosure fail, (ii) there is a high probability of irreversible or fatal harm to the relative, (iii) the disclosure of the information will prevent harm, (iv) the disclosure is limited to the information necessary for diagnosis or treatment of the relative, and (v) there is no other reasonable way to avert the harm"* (14).

In the case we have presented, there is no third party under risk since the patient's disease status poses no risks for the potential husband. Therefore, the physician in charge does not have a duty to inform him.

However, at this point a moral conflict for the family arises; namely, whether to inform the future husband about the genetic condition. The tendency to hide this information from the future husband may be related with a fear of refusal and cancellation of the marriage process, which may create significant social pressure both on the woman and her family, particularly in the Turkish community. When information about the genetic disease is learned by the public, it has a significant potential to cause social harm for the family. However, when the issue is considered with regard to the moral obligations of a couple towards each other, it becomes obvious that the genetic condition of one person may have a significant impact on the future life of the other for a number of reasons.

First, if the couple plans to have children, then both parties have a duty to disclose information that may potentially affect the welfare of their child. Second, genetic testing may play an important role in marriage even in the absence of children. For instance, one spouse may need to provide care permanently for the other in the future. Therefore, even if no risk of genetic harm is concerned, the future spouse is considered to be entitled to information (18).

In the study by Klitzman and Sweeney (19), disclosing genetic information to the partner has been justified due to moral obligations, disease in the family and the impact on children, whereas fear of refusal by the partner was detected to be an underlying reason for withholding information. Furthermore, participants in the study agreed that individuals need to disclose information on the basis of expectations arising from mutual trust and it was emphasized that such disclosure should take place before the marriage.

The moral aspects of disclosing to or withholding genetic information from the potential spouse can also be examined in the context of virtue theory. Aristoteles has asserted that virtuous action does not lead to a virtuous character; rather, it is the good character that gives rise to virtuous behavior. According to Aristoteles, virtue is the excellence of character and the fundamental question in virtue ethics deals with what the person should "be" instead of what the person should "do" (20). Therefore, in public life we appreciate honest, just, respectful persons and we condemn dishonest, unfair, malevolent individuals. Rather than the performance of a list of specific duties, virtues theory involves doing what is good as an extension of a virtuous moral character. Since virtues play a significant role in human relationships involving intimacy and dependency, they are relevant in a case where two individuals are planning to marry. Although the 19-year old patient can be considered to be under the pressure of her family, she has made a choice. Aristoteles acknowledges this aspect of choice as in the following: "We have the option of not doing the things that we are capable of doing; similarly, we have the options of saying "yes" to things which we can say "no" to. Humans are the initiators and the causes of their own actions as well as their children (20).

Therefore, from the perspective of the virtue theory it can be asserted that genetic information must be disclosed despite the fear of refusal especially if there is mutual trust between the parties. On the other hand, it should also be noted that women are in a fragile status against physical, social, psychological and economic abuse. Therefore, how the individual will use her genetic information will still depend on the culture she lives in.

In addition, Wertz, Fletcher and Berg prepared guidelines on behalf of the World Health Organization (WHO) in 2003 entitled "Review of ethical issues in medical genetics". The guidelines emphasize the importance of encouraging the individuals for the disclosure of genetic information to the partner (18).

Questions: Does the fact that the patients is responsible for taking care of her 6-year old brother mean that she is entitled to act as a decision-maker on his behalf? Is the 6-year-old brother being used as a means to an end? If genetically testing the 6-year old brother is of vital importance for the patient, would this be enough to justify the use of the test on her brother?

Genetic Tests and Vulnerable Groups

The patient's brother in our case is a 6-year old child. Written regulations state that genetic test for minors and for adults who lack the capacity to consent can be ethically justified only in circumstances where such testing will have a significant impact for the benefit and the health of the individual (21).

Vulnerable groups are synonymous with groups under risk. They consist of individuals who can easily be harmed since they lack the means and the capacity to protect themselves and their rights. Persons can become vulnerable for various reasons. For instance, the elderly, individuals with disabilities and immigrants can all be considered vulnerable. Children are also a vulnerable group and they are considered vulnerable on the basis of their age, regardless of their social status (22). They usually can not foresee the consequences of their actions and cannot think in long terms on their future. Parents are therefore considered as decision makers at this point. The decisions they make are required to involve the best interests of the child. In addition, experts suggest that relevant information that is closely related with and has the potential to have a significant impact on the future of the child be provided so that the child can develop in a supportive and caring environment (21).

The genetic testing in the case we have presented is to be performed on a 6-year old child with Down syndrome receiving physical therapy and special education. Although the patient herself claims that "she is responsible for caring for her brother", the parents are the legal guardians of her brother. The test itself is not expected to provide a direct benefit for the child; it would primarily benefit the patient. In the context of Kantian ethics, this would be considered as an example of using a human being as a means to an end. For this reason, Kantian ethics would strongly oppose the testing of the 6- year old brother, since this would mean that a human being would be used merely as a means to benefit another person (23). While no serious harm to the child is expected to occur as a result of testing, this would not be adequate to justify this course of action in Kantian ethics, where the moral status of the action does not depend on its consequences. The action in question involves an intent to use a human as a means to an end and therefore; it is unethical regardless of its potential outcomes.

Last but not least, as noted in the beginning of the article, genetic information involves not only the individual person but also the family as a whole. For this reason, communitarian ethics as an approach that considers the benefits of other family or community members involved also provides a significant alternative for examining the case. Communitarian ethics asserts that every individual making up a community is valuable and the best course of action should involve the good of the whole community. The basic premise of communitarians is that individuals are socially constructed and that belong to larger social structures such a family, tribe, clan and nation through social bonds (24).

CONCLUSION

As a result, individuals may choose to respect a moral value or may disregard it through their actions. Therefore, actions must always be based on the "knowledge of human values" (25). The first step of correct evaluation of an action in an ethical context is the delineation of the reasons for that particular action by the individual and the determination of the value of the action that has been performed or avoided (9) and in the context of particular cases, this is only

possible by presenting a justification of the approach taken to deal with the moral conflict at hand.

In the case we have presented, promoting one particular decision as the single correct course of action does not seem possible. For this reason, we have chosen to present the justifications of various approaches that could provide guidance for the health care professionals. At first, the responsibilities of the professional may seem clear. The 19-year-old patient is legally entitled to demand the test and there is no justification to limit her access to this service. Similarly, testing the 6-year-old brother without the family's permission in order to determine the genetic map of the patient would also be unlawful and unethical. However, other courses of actions presented in the text, along with their justifications that consider the unique details of the particular case, can be helpful for the professionals by providing different perspectives on the issue.

Conflict of interest

No conflict of interest was declared by the authors.

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