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Understanding and managing patients with adult rare diseases

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Despite advances in the diagnosis and management of rare diseases (RDs), there remains a tendency to overlook adult RD patients. In addition to the considerable number of adult-onset RDs, advances in the diagnosis and management of pediatric RDs have led to an increase in the survival of these patients into adulthood. Adult RDs exhibit distinct features from pediatric counterparts, necessitating careful consideration during medical assessments. Given the extended life expectancy of adult RD patients, precise diagnosis and management strategies can significantly enhance patient outcomes. This review aims to provide an in-depth exploration of the characteristics unique to adult RDs. Special emphasis will be placed on the importance of cascade screening and prenatal genetic testing in the context of adult RDs, highlighting the need for a comprehensive understanding of these aspects in clinical practice.

Key words: Rare diseases, Late onset disorders, Genetic diseases, inborn, Genetic carrier screening, Genetic counseling.

Introduction

Rare disease (RD) can encompass heterogeneous conditions that affects a small percentage of the population [1]. Although each RD typically involves a small number of patients, there are approximately 7,000 identified RDs to date, collectively affecting nearly 10% of the world's population [2]. Seventy percent of all RDs are genetic, arising from both germline and somatic gene mutations. Among RDs with a genetic origin, the majority follow a monogenic pattern following Mendelian inheritance principles [3]. However, some RDs arise from non-genetic causes, such as infections, nutritional deficiencies, and autoimmune responses [4-6].

RDs are generally defined based on prevalence; however, the definition of RD differs among countries. In the U.S., the Orphan Drug Act defines an RD as one that affects fewer than 200,000 people in the country, while the European Union defines RDs as those that affect fewer than 1 in 2,000 people [7]. In Korea, RDs are defined as diseases affecting fewer than 20,000 individuals [8]. The precise prevalence of RDs in Korea remains unknown, but it is estimated that over 500,000 individuals suffer from RDs in the country [9].

Among RDs, 70% are exclusively pediatric onset, 20% have onset spanning both pediatric and adult stages, and 10% are exclusively adult onset [1]. Although approximately 30% of children with RDs face mortality before reaching the age of 5 years, some RDs transform into chronic conditions, leading to lifelong disabilities [10]. RDs that manifest in late-adulthood are entirely different types of conditions from pediatric RDs [11]. Therefore, adult RD patients exhibit characteristics distinct from

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those observed in pediatric cases, underscoring the importance of understanding these features and providing appropriate care. This review aims to elucidate the unique characteristics of adult RDs and highlight crucial issues in the clinical care of adult RD patients.

General Characteristics of Adult Rare Disease Patients

Adult RD patients can be divided into two categories. The first category involves individuals who were diagnosed with RDs during childhood, and as they become adults, they continue to face the challenges associated with their condition. The transition from pediatric care to adult healthcare settings requires careful consideration of the unique needs of these patients, as the manifestation and management of RDs may evolve over time [10]. Owing to the advances in the diagnosis and management, and especially due to recent breakthroughs in RD therapeutics, individuals transitioning from childhood to adulthood with RDs are anticipated to increase in the future [12]. For example, Nusinersen has increased the survival rate of individuals with Spinal Muscular Atrophy, leading to more patients reaching adulthood [13]. Understanding the continuum of RDs from childhood to adulthood is crucial for providing comprehensive and effective medical care to this growing population [14].

The second category of patients with adult-onset RDs tends to experience a longer diagnostic odyssey than those with pediatric RDs [15,16]. This is because adult-onset RDs often exhibit a wide spectrum of highly variable and heterogeneous symptoms. Adult RD patients may present with nonspecific or common disease-like symptoms, insidious onset with subtle manifestations that progressively worsen over time, and a complex interplay of genetic, environmental, and other factors that make accurate diagnosis more challenging [17].

However, it is noteworthy that adult RD patients frequently exhibit symptoms not directly linked to a life-threatening condition, resulting in a longer life expectancy when seeking medical attention [17,18]. Therefore, achieving an accurate diagnosis becomes crucial, as it can bring significant positive changes to the remaining lifespan of the patient. Although there is no cure for the disease, in some cases, there is an opportunity to prevent the transmission of the disease to the next generation through genetic counseling and appropriate testing [19].

Another characteristics of adult RDs are higher proportion of non-genetic causes than in the pediatric population. Environmental exposures, lifestyle variables, and immunological etiologies may contribute to the occurrence of adult RDs [2]. This complexity manadates a holistic diagnostic paradigm that integrates genetic and non-genetic considerations. Interdisciplinary collaboration and access to specialized expertise become crucial in unraveling the intricate symptomatology of adult RDs [20]. Additionally, the psychosocial impact of living with a RD, compounded by the uncertainty surrounding diagnosis and prognosis, adds an additional layer of complexity that necessitates a holistic approach to patient care [21].

Drug Repurposing and Dietary Modification

Drug repurposing, also known as drug repositioning, is the process of redeveloping a compound for use in a different disease and is now becoming an increasingly important strategy for RDs [7]. Developing new therapies for RDs is particularly challenging and time-consuming due to the limited patient population, making it difficult to justify the costs and time associated with creating entirely new drugs. Additionally, many RDs are life-threatening, and patients may not survive prolonged clinical trials. Therefore, drug repurposing emerges as a more cost-effective and time-efficient solution [22,23]. By leveraging compounds that have already undergone rigorous testing, researchers can expedite the drug development process and potentially uncover novel treatments for rare conditions.

One of the most remarkable examples is the repurposing of mexiletine for treating skeletal muscle channelopathies, including nondystrophic myotonia such as paramyotonia congenita and myotonia myotonia congenia [24]. Mexiletine is initially developed as an antiarrhythmic medication, and its membrane-stabilizing capacity has proven beneficial in alleviating the abnormal muscle excitability characteristic of these channelopathies. As a sodium channel blocker, mexiletine specifically helps regulate muscle cell membrane potential, thereby alleviating symptoms of muscle stiffness. Consequently, mexiletine can significantly improve the quality of life for patients who have suffered from myotonia symptoms since birth [25]. This exemplifies how exploring alternative applications for existing drugs can provide valuable therapeutic options for individuals with RDs, where treatment choices are limited.

Dietary modification proves to be profoundly beneficial in specific RDs, particularly those caused by metabolic enzyme deficiencies. Adjusting nutrient intake can help mitigate symptoms and promote overall well-being in individuals with these conditions [26]. Very-long-chain acyl-CoA dehydrogenase deficiency is a rare genetic disorder that makes the body unable

to break down certain fats, leading to energy production issues. It often manifests as recurrent rhabdomyolysis in its adult-onset form. Dietary modification in these patients involves a meticulous balance of carbohydrates and fats, coupled with the restriction of long-chain fatty acids [27]. Similarly, carnitine palmitoyltransferase II deficiency, disrupting the fat utilization during increased energy demands, results in exercise-induced muscle pain and weakness in adults. Dietary adjustments are crucial, emphasizing the necessity to regulate fat intake, ensure sufficient carbohydrates, and to prevent energy depletion [28]. Dietary modifications are designed to optimize energy metabolism, alleviate symptoms, and improve the overall quality of life for those affected by these specific rare metabolic disorders.

Cascade Screening

Cascade screening is a medical approach used to identify individuals at risk for a genetic disorder. This method involves systematically testing the relatives of an individual who has been diagnosed with a specific genetic condition [29]. Cascade screening plays a pivotal role in the context of adult RDs, especially those with a genetic basis. Adults with RDs often develop symptoms after getting married and having children, so there is a possibility of another patient emerging within the family. By tracing the familial thread of a RD, cascade screening has significant implications for early detection, intervention, and the implementation of targeted preventive measures [30].

By identifying individuals who have inherited the genetic predisposition to a RD, doctors can implement preventive measures, initiate monitoring, and provide timely interventions to mitigate the impact of the condition. For instance, in the case of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), cascade screening enables the identification of asymptomatic carriers, allowing for extensive control of vascular risk factors [31]. This involves blood pressure management, cholesterol monitoring, and lifestyle modifications, contributing to enhanced disease management and improved patient outcomes.

It is crucial for healthcare professionals to provide a comprehensive and clear explanation to individuals undergoing cascade screening, ensuring they fully understand the purpose, process, and potential outcomes of the screening. In cases where there are no treatment options for the identified condition, the significance of informed consent becomes even more pronounced [30].

In addition, testing minors who are at risk of certain RDs poses ethical considerations since they may lack the capacity to fully comprehend the risks and benefits of testing or make independent decisions about testing [32]. Receiving a diagnosis of being a carrier of certain rare genetic diseases during childhood can be a challenging and overwhelming experience for both the child and their family [33]. Consequently, unless they exhibit symptoms of a RD, it is generally advisable to defer predictive testing until they reach adulthood.

Prenatal Testing and Preimplantation Genetic Testing

Understanding the inheritance patterns in genetic RDs allows individuals to make informed decisions about having children. It also provides an opportunity opens up opportunities to explore reproductive options [34]. In Korea, more than 200 specific genetic disorders are eligible for genetic testing on fetuses or embryos have been designated by law, and the list of such diseases is continually expanding [35,36]. Most of these disorders lack available treatments and exhibit severe symptoms. For these conditions, prenatal testing or preimplantation genetic testing (PGT) can be applied [34,37]. Prenatal testing includes chorionic villus sampling and amniocentesis which can detect genetic abnormalities of the fetus during pregnancy. PGT involves the genetic analysis of embryos created through *in vitro* fertilization before implantation, enabling the selection of embryos free from specific genetic mutations associated with RDs. However, as these testing methods are not 100% accurate, a thorough genetic counseling process is crucial to adequately inform patients and their families [34]. Particularly, when prenatal diagnosis reveals a genetic disorder or chromosomal abnormality in the fetus, ethical considerations arise, as the option of therapeutic abortion may need to be considered. This not only poses ethical dilemmas but also involves significant mental and physical challenges associated with pregnancy termination [38].

Huntington's disease (HD), an autosomal dominant neurodegenerative disorder, stands as a notable example for implementing prenatal testing or PGT [38,39]. HD is caused by expansion of CAG repeat in the *HTT* gene and typically manifest in individuals between the ages of 30 and 50 years. Although the offsprings of HD patient have 50% chance of inheriting the devastating disease, there is an opportunity to ascertain their inherited status before the appearance of any symptoms. However, as previously mentioned, diagnosing a disease without a cure during the presymptomatic stage can pose a significant psychological burden. Consequently, the implementation of cascade screening for HD

warrants careful consideration. Nevertheless, if the offspring of individuals with HD are considering marriage or parenthood, it is essential to emphasize that determining their carrier status is crucial [39]. This information enables the prevention of disease transmission to the next generation through prenatal testing or PGT. Healthcare professionals should provide sufficient information to individuals, guiding them to make decisions based on their own judgment.

Conclusion

Adult RDs exhibit distinct characteristics compared to pediatric RDs. Therefore, understanding these unique aspects is important in patient care. Given the longer life expectancy associated with adult RDs, precise diagnosis provides opportunities such as drug repurposing. Moreover, cascade screening is vital for the early detection of patients within family members, and prenatal genetic counseling is crucial for preventing the transmission of RDs to subsequent generations. Healthcare professionals should pay more attention to adult RDs, which will eventually enhance patient care.

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