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ORIGINAL ARTICLE

Researching Fabry Disease in Autosomal Dominant Polycystic Kidney Disease Patients

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Abstract

Aim: This study aims to determine the frequency of Fabry disease misdiagnosis with autosomal dominant polycystic kidney disease (ADPKD). Additionally, the study aims to characterize the clinical and biochemical features of Fabry disease patients initially diagnosed with ADPKD.

Method: Thirty-six patients diagnosed with ADPKD, based on family history and radiological criteria, who were regularly followed up at the Uludag University Nephrology Clinic, were enrolled in this single-center cross-sectional study. All participants provided written informed consent. A 10-cc peripheral blood sample was collected from each participant during their regular follow-up. The GLA gene sequence analysis was performed using the MiSeq next-generation sequencing (NGS) platform, an FDA-approved diagnostic system (Illumina, San Diego, CA, USA). This study was approved by the local ethics committee and was conducted under the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment in the study. Confidentiality and privacy of the participants were ensured throughout the study.

Results: In line with the study's design, only Fabry disease mutations were investigated in the patients. Of the 36 participants, 35 had normal results regarding Fabry disease mutations, while one patient was positive for Fabry disease mutation.

Conclusion: Our study was limited by its focus solely on investigating Fabry disease mutations and the relatively small sample size; our results suggest that patients with ADPKD should consider Fabry disease as a differential diagnosis to ensure proper diagnosis and management of their condition. Further research with a larger sample size is necessary to understand our findings' clinical implications fully.

Keywords

Fabry disease, Autosomal dominant polycystic kidney disease, Kidney cyst

Introduction

ADPKD is a hereditary renal disorder characterized by the formation of numerous fluid-filled cysts in the kidneys. The cysts arise from various segments of the nephron and can range in size from microscopic to several centimeters in diameter. Two genes are associated with ADPKD: PKD1 and PKD2. Mutations in the PKD1 gene are more common and are generally associated with a more severe form of the disease. Mutations in the PKD2 gene are less common and generally associated with a milder form of the disease. The PKD1 and PKD2 genes provide instructions for making proteins called polycystin 1 and polycystin 2, respectively. These proteins are essential for the normal functioning of tubular cells, and mutations in these genes can disrupt the typical structure and function of tubular cells, leading to the development of cysts in the kidneys [1].

The cysts in ADPKD are lined with epithelial cells that exhibit abnormalities in the expression and function of polycystin-1 and polycystin-2, which are integral proteins that regulate intracellular calcium and other signaling pathways. As a result, cell proliferation changes, fluid secretion in cells increases, and defective apoptosis occurs. Accumulation of fluid in the cysts leads to pressure increases in the kidney, interstitial fibrosis, and inflammation, and it causes progressive kidney damage. Although the level of kidney damage is variable, most patients with the disease develop hypertension, proteinuria, and eventually ESRD. Apart from the kidney, disorders, and cysts may occur in the liver, pancreas, and cardiovascular system, especially

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in the heart. Liver cysts are common in these patients and may cause hepatomegaly, abdominal pain, and liver failure. Left ventricular hypertrophy with or without hypertension is a common disorder in the cardiovascular system. Brain aneurysms are found in 10% of patients and can cause morbidity and mortality in case of bleeding. In the world, 10% of ESRD patients are ADPKD patients. Due to these reasons, early diagnosis and follow-up of this disease, which causes much mortality and morbidity due to renal or extra-renal causes, is essential worldwide [2].

Fabry disease (FD) is a progressive, X-linked inherited disorder of glycosphingolipid metabolism due to deficient or absent lysosomal α-galactosidase A activity. This results in various systemic manifestations, including neuropathic pain, cardiovascular disease, renal insufficiency, and cerebrovascular disease. FD is pan-ethnic, and the reported annual incidence of 1 in 100,000 may underestimate the true prevalence of the disease. The classic form of Fabry disease occurs in males and is characterized by the onset of symptoms during childhood or adolescence, including acroparesthesias, angiokeratomas, corneal opacities, and hypohidrosis. In contrast, the late-onset form of Fabry disease can affect both males and females and is characterized by a more gradual onset of symptoms, typically in adulthood. These symptoms can include renal dysfunction, cardiomyopathy, and cerebrovascular disease. While Fabry disease and autosomal dominant polycystic kidney disease (ADPKD) are distinct disorders characterized by different genetic mutations, they share specific clinical manifestations such as renal cysts and the development of left ventricular hypertrophy (LVH). Alpha-galactosidase A (AGAL) enzyme activity level is considered the gold standard for diagnosing Fabry disease. In fabry patients its activity is significantly reduced or absent. Also searching for genetic mutation in AGAL gene is another way of diagnose. Fabry disease can be treated with three different modalities: Chaperone therapy, substrate reduction therapy (SRT), and enzyme replacement therapy (ERT). With chaperone therapy, some faulty forms of alpha-galactosidase-A can be corrected and delivered to the lysosomes so that the excess Gb3 can be broken down. SRT employs small molecules to inhibit Gb3 synthesis, thereby reducing the burden of substrates on residual α-Gal A. ERT involves the intravenous infusion of recombinant α-Gal A to compensate for the deficient enzyme. The presence of renal cysts in ADPKD patients can pose challenges in diagnosing Fabry disease, as renal cysts are also a common feature of ADPKD. LVH, a common finding in ADPKD and Fabry disease, amplifies the risk of cardiovascular complications, including heart failure, arrhythmias, and sudden cardiac death. Early detection and management of LVH are crucial in individuals with either of these conditions. Therefore, healthcare providers should consider Fabry disease as a differential diagnosis in patients with ADPKD who present with symptoms such as neuropathic pain, gastrointestinal symptoms, cardiovascular complications, and renal cysts [3-6].

Materials and Methods

Our study was conducted on patients who were being regularly monitored at our hospital's Nephrology Clinic, aiming to investigate various factors related to their health. During their routine follow-up visits, we collected important demographic information including age, gender, height, weight, family history, and presence of any coexisting diseases. Additionally, we retrospectively examined several biochemical markers such as serum urea, creatinine, electrolyte levels, complete blood count, as well as alanine transaminase and aspartate aminotransferase values. Vital signs, such as blood pressure and heart rate, were also recorded during outpatient clinic visits.

To ensure the reliability of our findings, we recruited patients who willingly agreed to participate in the study and signed the informed consent form. For the purpose of genetic analysis, we collected 10 cc blood samples from each participant using EDTA tubes. The DNA isolations were carried out using 200 µl of peripheral blood samples obtained from the individuals, and these samples were carefully stored at -200 °C until the subsequent polymerase chain reaction (PCR) stage. The QIAamp DNA Blood Mini Kit from Qiagen Inc. was utilized for efficient DNA extraction.

To specifically analyze the GLA gene, which is known to be associated with certain genetic disorders, we designed seven pairs of PCR primers using PRIMER© - Primer Designer v.2.0 software. The PCR products were then purified using the NucleoFast® 96 PCR kit from MACHEREY-NAGEL GmbH. Following the purification step, sequencing reactions were performed using both forward and reverse primers. The resulting products were further purified using the ZR-96 DNA Sequencing Clean-up Kit from Zymo Research Corp., according to the manufacturer's protocol. Capillary electrophoresis was conducted utilizing the ABI 3130 capillary electrophoresis system from Applied Biosystems Inc., following the standard procedures.

In order to analyze the obtained sequences and identify any potential sequence variations, the sequences were aligned to the hg19 genome within MiSeq Reporter software developed by Illumina Inc. Furthermore, the data were visualized and examined using the Integrative Genomics Viewer (IGV) 2.3 software, a powerful tool provided by the Broad Institute. Finally, the SeqScape 2.5.0 software, developed by Applied Biosystems Inc., was employed to perform comprehensive analysis and identify any relevant sequence variations that may contribute to the development of Fabry disease.

The incorporation of next-generation sequencing (NGS) technology in our study allowed for a highly efficient and accurate analysis of the GLA gene, providing valuable insights into the molecular basis of Fabry disease. By examining the genetic variations within our study population, we aimed to shed light on the pathogenesis of this disorder and emphasize the importance of early diagnosis and treatment in improving patient outcomes.

Results

The study was designed as a single-center, prospective study to investigate the prevalence of Fabry disease mutations in patients with ADPKD. A total of 36 volunteers were included in the study, with 20 females and 16 males and an average age of 42.25 years. Twenty-six patients are diagnosed by computer tomography, while ten patients are diagnosed by ultrasonography. None of the patients had undergone dialysis treatment. In the retrospective analysis of laboratory values, the average serum uric acid level was found to be 4.97 (± 1.50) mg/dL, the average serum creatinine level was 0.73 (± 0.88) mg/dL, the average serum albumin level was 4.29 (± 0.32) g/dL, the average hemoglobin level was 12.73 (± 1.7) g/dL, the average serum cholesterol level was 192 (± 40.73) mg/dL, the average HDL cholesterol level was 38.5 (± 7.8) mg/dL, the average LDL cholesterol level was 78.50 (± 110) mg/dL, and the average serum triglyceride level was 161.6 (± 104.11) mg/dL.

Following the study's design, the investigation focused solely on identifying Fabry disease mutations in the cohort of ADPKD patients. Out of the 36 participants, only one patient was identified to have a positive result for Fabry disease mutation, while the remaining 35 individuals had normal results.

Our Suspected Patients History

64-year-old male patient with a history of proteinuria since 2014 was monitored over time. Initially, his creatinine level was measured at 1.2 mg/dL, with proteinuria of 1 g/day. Subsequently, in 2018, the patient exhibited an elevated creatinine level of 1.6 mg/dL and increased proteinuria of 1.4 g/day. Renal ultrasonography revealed extensive cystic formations in both kidneys. Additionally, a familial association with proteinuria and prior corticosteroid therapy was observed in a cousin.

In terms of proteinuria evaluations, the patient's thyroid-stimulating hormone (TSH) levels were found to be 1.5 mIU/L, and tests for antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), complement components C3 and C4, as well as immunoglobulins (IgG, IgA, IgM) demonstrated values within the normal range. Negative results were obtained for hepatitis B surface antigen (HBsAg), human immunodeficiency virus (HIV), and anti-hepatitis B core antibody (Anti-HbC) tests.

A specific test for Fabry disease was conducted, revealing a hemizygous mutation NM:000169.2c.937G > T(p.Asp313Tyr) in the GLA gene [7-9]. Furthermore, the alpha-galactosidase enzyme level was quantified as 3.8 mmol/mL/hour, exceeding the normal threshold (considered normal if above 2.5 mmol/mL/hour). Despite the enzyme level being within the normal range, continued patient monitoring was warranted due to clinical manifestations and suspicious family history.

Unfortunately, while the patient's investigations were ongoing, he died because of lung adenocarcinoma.

Conclusion

The primary objective of our study was to investigate the prevalence of Fabry disease mutations in a specific group of patients diagnosed with kidney cysts. While autosomal dominant polycystic kidney disease (ADPKD) is commonly associated with kidney cysts, it is important to consider the possibility of Fabry disease due to its potential presentation with similar symptoms and its treatable nature. Identifying a Fabry disease mutation in a patient initially diagnosed with kidney cysts highlights the need for cautious clinical evaluation and genetic testing to avoid misdiagnosis and ensure appropriate management [10].

By focusing on the potential correlation between ADPKD and Fabry disease, our study aimed to contribute to the understanding of these two genetic disorders and their comorbidity. Exploring the relationship between these conditions could provide valuable insights into the underlying mechanisms and clinical implications. It is crucial not to overlook the possibility of Fabry disease in the differential diagnosis of kidney cysts, particularly in patients with a family history of kidney disease [10].

Early diagnosis of Fabry disease in patients with kidney cysts is of paramount importance as it can significantly impact patient outcomes. Timely identification allows for appropriate interventions and personalized treatment strategies, ultimately leading to improved management of the disease and better patient prognosis.

Overall, our study underscores the significance of considering Fabry disease in patients presenting with kidney cysts and highlights the need for further research to elucidate the relationship between ADPKD and Fabry disease. By enhancing our understanding of these conditions, we can optimize diagnostic approaches and therapeutic interventions, ultimately benefiting patients affected by kidney cysts and related genetic disorders [10].

Conflict of Interest

Genetic tests are funded by Intergen Genetics and Rare Diseases Diagnosis Center.

References

1. Torres VE, Harris PC, Pirson Y (2007) Autosomal dominant polycystic kidney disease. The Lancet 369: 1287-1301.
2. Chebib FT, Torres VE (2016) Autosomal dominant polycystic kidney disease: Core curriculum 2016. Am J Kidney Dis 67: 792-810.
3. Alroy J, Sabnis S, Kopp JB (2002) Renal pathology in Fabry disease. J Am Soc Nephrol 13: S134-S138.
4. Brady M, Montgomery E, Brennan P, Mohindra R, Sayer JA (2015) Diagnosing Fabry disease--delays and difficulties within discordant siblings. QJM 108: 585-590.
5. Germain DP (2010) Fabry disease. Orphanet J Rare Dis 5: 30.
6. Yousef Z, Elliott PM, Cecchi F, Escoubet B, Linhart A, et al. (2013) Left ventricular hypertrophy in Fabry disease: A practical approach to diagnosis. Eur Heart J 34: 802-808.
7. Niemann M, Rolfs A, Giese A, Mascher H, Breunig F, et al. (2012) Lyso-Gb3 Indicates that the Alpha-Galactosidase A Mutation D313Y is not Clinically Relevant for Fabry Disease. JIMD Rep 7: 99-102.
8. Monserrat L, Gimeno-Blanes JR, Marín F, Hermida-Prieto M, García-Honrubia A, et al. (2007) Prevalence of fabry disease in a cohort of 508 unrelated patients with hypertrophic cardiomyopathy. J Am Coll Cardiol 50: 2399-2403.
9. Koulousios K, Stylianou K, Pateinakis P, Zamanakou M, Loules G, et al. (2017) Fabry disease due to D313Y and novel GLA mutations. BMJ Open 7: e017098.
10. Linthorst GE, Bouwman MG, Wijburg FA, Aerts JMFG, Poorthuis BJHM, et al. (2010) Screening for Fabry disease in high-risk populations: A systematic review. J Med Genet 47: 217-222.