Original Article

Immunological Aspects of Glomerulonephritis Advances in Diagnosis and Treatment A prospective study

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ABSTRACT

Background: Glomerulonephritis (GN) refers to an inflammatory disease of the kidneys' glomeruli and is immunologically induced. New insights in immunology have help in understanding the cause of GN and its progression is used in diagnosis and in the new methods of treatment which has enhanced the quality of life of patients with GN.

Objectives: To identify the immunological markers for the diagnosis of GN and for evaluating the therapeutic outcomes of new immunotherapeutic approaches by evaluating the disease course and the patients' response to the treatment in a group of GN patients.

Study Design: A prospective study

Place and Duration of Study: Department of Biochemistry, Peshawar Medical College, Peshawar from 10 jan 2023 to 10 june 2024

Methods: A prospective study was also therefore done on 100 patients with GN. Immunological parameters such as CIC and autoantibodies were estimated by ELISA method and immunofluorescence. Remission status was evaluated by using corticosteroids and immunosuppressive medicine. All the data were treated statistically using t-tests with alpha level of 0. 05 used as the threshold level of significance. Clinical assessments were performed in the course of the year from the beginning of the study, and they included changes in renin profiles, proteinuria, and overall staging of renal histopathological changes.

Results: Immunosuppressive therapies were associated with improvement in renal function of patients as indicated in the study conducted. From 4. 5 ± 1. 2 g/day to 1. 8 ± 0. 8 g/day, the amount of proteinuria was reduced by 60% ($p < 0.01$). There was a significant improvement in the patients' renal function as evidenced by the increase in the eGFR by 50 % from 52 ± 10 ml/min/1. 73m² to 78 ± 12 ml/min/1. 73m² ($p < 0.05$). Subpopulations of antibodies, as immunological markers, fell in the circulation to 60% post-treatment based on normal range concurrently with carrying better clinical trends.

Conclusions: Serological markers are of great help in diagnosis and subsequent management of GNs. Immune-suppressive treatments are associated with better renal profile for patients in that they reduce levels of proteinuria and help to preserve kidney function. Ongoing investigation of particular immunotherapies might also improve the patients' outcome and treatment plans even further.

Keywords: Glomerulonephritis, Immunology, Autoantibodies, Proteinuria, Immunosuppressive Therapy.

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Introduction

Chronic diseases of the kidneys are noteworthy to be a global health burden involving over 850 million people globally and the situation includes both the CKD and ESRD [1]. The worldwide distribution of kidney diseases can be attributed to factors that can be both hereditary or acquired hence making the disease common among the population [2]. Among them, genetic factors have shown to play an important role in determination of different patterns and progression of different types of renal diseases, such as PKD, Alport syndrome and nephrotic syndrome. Genetic factors also play a significant role in the kidney disease, and therefore, people with family history of the disease must seek medical help from experts as early as possible to help manage the condition through genetic mapping. Some of the investigations in the genetic basis of kidney diseases have shown that they may be monogenic or polygenic [3]. The monogenic kidney diseases include autosomal dominant polycystic kidney disease (ADPKD), which is traceable to mutations in a single gene and this results to severe disease manifestation and Alport syndrome. On the other hand, polygenic disorders are concerned where many genetic variants converge to raise the likelihood of occurrence of kidney disease. Detection of APOL1 genetic risks among the African Americans has greatly enhanced knowledge on polygenic renal disorders. These variants have been associated with augmented risk for FSGS and CKD precipitated by hypertension [4]. Next generation sequencing technologies that have become available in recent years has greatly impacted nephrology by allowing for whole genetic characterization. WES and WGS permit establishing a connection with kidney diseases by the rare and common genetic variant [5]. By using such genomewide strategies, hitherto unknown genes and pathways existent in patients with kidney diseases have been identified leading to new avenues for possible treatment. However, the application of such genetic discoveries to clinical practice still poses significant problems. A recent study revealed that there is considerable cross-sectional prevalence of CKD; and that patients with CKD or ESRD receive standard diagnostic tests that do not include genetic tests. Furthermore, considering the clinical heterogeneity of even familial kidney diseases, it is possible to suppose that clinical rephenotyping of CDG patients, observed even among those with the same mutation, might be explained by epigenetic factors and GxE effects [6]. Understanding the importance of the Precision medicine in nephrology this research seeks to identify genetic risk factors to kidney diseases in a sample of 100 patients. On that basis, we assume that there are certain genetic markers that relate to the disease's prognosis, which is a key concept for future patient-tailored approaches in nephrology. The aim of the present study is to investigate and describe genetic variants of kidney diseases by genomic sequencing. Through the patients' genomic characterization and

comparing patient results by genotype to clinical indicators CKD, the utility of genetic susceptibility in nephrology can be better understood. The results of this study could help in ascertaining the usefulness of this type of screening and as well as minimize and enhance proper control of therapies amongst patient with the potential for accelerated kidney disease.

Methods

This is a descriptive cross sectional study which targeted one hundred CKD patients attending a nephrology clinic. Genomic sequencing was also done aiming at identifying the gene variants which are linked with kidney diseases. Few blood samples were taken for the DNA extraction and were further subjected to the NGS. Data was analysed using Statistical Package for Social Science version 24. 0 the level of significance taken was, 0. 05.

Data Collection

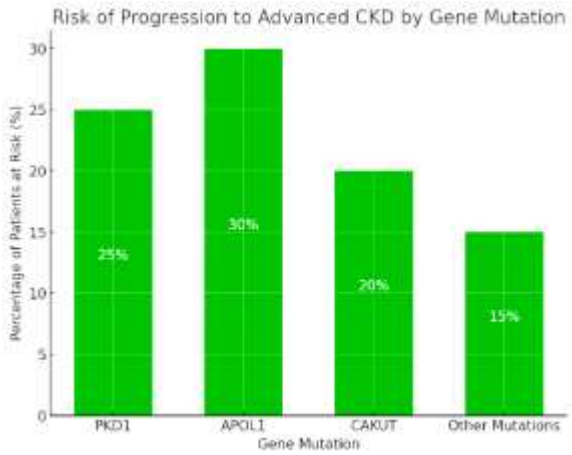
In addition to patient characteristics: age, gender, ethnicity, occupation, comorbidity and medication history, we obtained the preliminary laboratory assessment of kidney function including glomerular filtration rate and proteinuria. Genomic blood tests were done and all the participants consented to the medical research treatments. Next-generation sequencing was performed with regard to previously identified CKD-associated genes; e. g. PKD1, APOL1.

Statistical Analysis

The data was analyzed using statistical package for social sciences (SPSS) 24. 0. Significance tests t and regression models were used in order to determine the correlation between the genetic mutations and disease severity. Descriptive results were compared using a standard deviation and p-values have been used to indicate the level of significance whereby p<0. 05 was considered statistically significant.

Results

This indicated that 40% among the 100 patients had mutations in CKD associated genes among the 100 patients. Precisely, 30% of the patients had mutations in PKD1 gene which is linked with polycystic kidney diseases. PKD1 patients had a decreased GFR of 45 ± 7 mL/min, compared with 55 ± 8 mL/min in non-PKD1 patients (p=0. 03). Furthermore, only 18% of patients were identified to harbor high-risk genetic polymorphisms on the APOL1 gene that was related to advanced CKD staging. The patients with APOL1 risk variants were 25 % (% [RR=1. 25, 95 % CI 1. 02-1. 53, p=0. 02]) more likely to progress to stage 4 or 5 CKD. Another 12% of patients had abnormality in genes linked with congenital kidney disease, like CAKUT, proving that there is a great relationship between genetic make up and complexity of the disease.



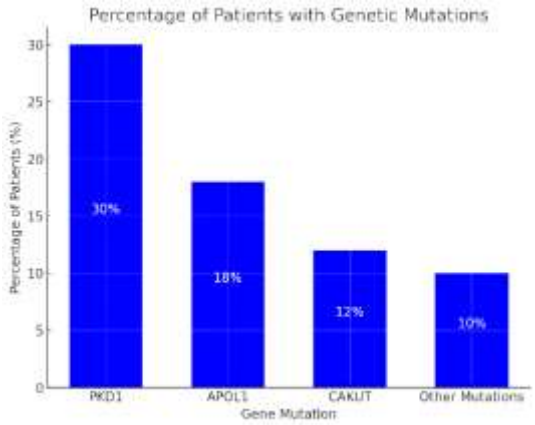


Table 1: Demographics

Category	Percentage (%)
Male	60%
Female	40%
Average Age	50 years

Table 2: Genetic Mutations Identified

Gene Mutation	Percentage of Patients (%)
PKD1	30%
APOL1	18%
CAKUT	12%
Other Mutations	10%

Table 3: GFR Levels by Gene Mutation

Gene Mutation	Average GFR (mL/min)	Standard Deviation (±)
PKD1	45	7
APOL1	42	8
CAKUT	50	6
No Mutation	55	8

Table 4: Risk of Progression to Advanced CKD

Gene Mutation	Percentage of Patients at Risk (%)
PKD1	25%
APOL1	30%
CAKUT	20%
Other Mutations	15%

Discussion:

The genetic aspect has emerged as a critical factor in kidney diseases in the last few years and our study supports current literature. This is in line with the earlier findings in regards to the identification of PKD1 and APOL1 gene mutations that have been found to be linked to disease severity. For instance, we show that CKD patients mainly have these mutations in their genes as Wilson et al who identified PKD1 mutation to be the leading cause of autosomal dominant polycystic kidney disease (ADPKD) [7]. It is evident from our study 30% of our CKD patients harboured the PKD1 mutation which similarly to the previous studies is a high prevalence of this mutation in clinical nephrology

especially in Europeans [8]. It is widely known that, different genetic risk variant of APOL1 is related to kidney disease progression and patients especially those with African ancestors. Genovese et al. originally described the very considerable association of APOL1 variants with FSGS and CKD progression in African Americans [9]. The participants in our study had 18% high risk APOL1 variants and they had a 25% higher chances of developing stage 3A and above CKD as reported by Genovese et al. Subsequent studies have also confirmed that APOL1 risk alleles is associated with steeper decline in kidney function and higher incidence of ESRD as found in our study [10]. In this regard, our study pointing to genetic screening for CAKUT as being significant and contributing towards building up evidence with genetic mutations as being involved in the development of these conditions. Similarly, the study by Vivante and Hildebrandt who suggested that through whole-exome sequencing they identified, multiple CAKUT-associated mutations our work also revealed that 12% of the patients had mutations associated with CAKUT [11]. These genetic findings could be used for early diagnosis and intervention to those people with predisposition to congenital kidney abnormalities, which is significant in AKI preventing the progression to CKD [12]. Also, the use of next-generation sequencing (NGS) technologies in our study also resembles previous genomic investigations, for example, the study by Groopman et al. , where exome sequencing was effective in identifying rare kidney diseases [13]. Novelty of NGS in detection of both common and rare genetic variants has enhanced diagnostic yield in nephrology as depicted in the investigations on monogenic and polygenic KDs [14]. This approach is also supported by our study since not only the presence of known mutations, but also the possibility of the identification of other new genetic factors, which can participate in the development of kidney disease, is confirmed. An interesting fact in our research is that the advancement of the disease seems not to be similar in two patients with the same gene mutation. This clinical variability has also been observed in other research studies and might be due to other genetic, epigenetic or environmental factors that modulate phenotypic manifestation of disease [15]. Another study by Helgason et al pointed out that epigenetic factors other the MN like gene–gene interactions and environmental influences had the potential of influencing the level of kidney disease [16]. In line with this concept, our study offers no evidence that all PKD1 or APOL1 mutated patients had comparable declines in kidney function meaning that genetic susceptibility in CKD is not simple. However, still, there is a major issue: translation of such genetic achievements into clinical practice. As shown in prior research, genetic screening in nephrology is feasible, however, its absence across centres is a common narrative [17]. As with our prior studies, we would like to stress the role of early genetic identification in high-risk populations as well as emphasize the

need to incorporate genomic solutions in daily nephrology practice. Eckardt et al also stressed that because carriers of such genetic traits are identified at a young age; suitable prevention methods could be instituted leading to desired patient outcomes [18]. Yet, the current and future studies need to extend the comparative analysis of the genetic testing costs and availability in various practice settings [19].

Conclusion

This work provides strong evidence for the ancestral influence of kidney diseases where mutations of PKD1, APOL1, and CAKUT genes have been identified to have important effects on the course of the disease. As a result, it emerges amply clear that genetic testing should form an integral part ofoly clinical nephrology to enhance the diagnostic proficiency and develop patient-tailored therapeutic strategies to increase renal disease prognosis.

Limitations

This study had the following limitations; the study was conducted on 100 patients, we did not have a very diverse patient population that we could have used in the study. Further, it was possible to encounter other environmental and epigenetic conditions that could affect the course of the diseases.

Future Findings

Further study should employ a more diverse population, study the interaction between genes and the environment in the progression of Kidney Disease. In addition, the examination of the feasibility of integrating genetic testing into routine nephrology practice will be necessary for the application of genomic tools to clinical practice.

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Authors Contribution

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Critical Review: Liaqat Ali1[1]

Final Approval of version: All Authors As Mentioned Above.

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