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Sickle cell nephropathy; exploring epidemiology, diagnostic challenges, and precision medicine advances

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Abstract

Sickle cell nephropathy (SCN) poses an important challenge in the realm of sickle cell disease (SCD) and sickle cell trait (SCT), especially impacting the pediatric population and progressing to chronic kidney disease (CKD) in adulthood. This review navigates through the epidemiology of SCN, emphasizing its variable clinical course and the age-related dynamics of onset. The intricate challenges in diagnosis are explored, highlighting the evolving landscape of early detection and treatment strategies. The prevalence of SCN is intricately linked to the global distribution of SCD and SCT, with higher incidences in regions where these conditions prevail. Diagnosing SCN presents significant challenges due to its variable clinical course, necessitating advanced imaging techniques and novel biomarkers. Promising biomarkers such as KIM-1 and MCP-1 show potential for early detection and intervention, addressing the limitations of conventional diagnostic methods. Precision medicine, focusing on genetic profiling, emerges as a crucial approach for risk stratification and personalized treatment plans. The multifaceted clinical manifestations of SCN, including hematuria, proteinuria, and hypertension, underscore the importance of timely intervention. Treatment strategies involve the administration of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, hydroxyurea for preventing chronic organ damage, and kidney transplantation for end-stage renal disease. Early diagnosis and intervention are critical to mitigate the progression of SCN and its associated complications, emphasizing the need for collaborative efforts in research and precision medicine to improve outcomes for individuals with SCN.

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Introduction

Sickle cell nephropathy (SCN) is a serious complication of sickle cell disease (SCD) and sickle cell trait (SCT), presenting a variable clinical course and age of onset (1,2). Particularly impactful in the pediatric population, SCN manifests with kidney dysfunction developing from childhood and progressing to chronic kidney disease (CKD) and kidney failure in adulthood (2,3). This review aims to comprehensively explore the epidemiology of SCN, emphasizing the intricate challenges in diagnosis, and highlighting the evolving landscape of early detection and treatment strategies.

Key point

Sickle cell nephropathy poses a significant health challenge, impacting pediatric populations and progressing to CKD in adulthood. The prevalence of SCN is linked to regions with higher incidences of SCD and SCT. Diagnosing SCN is complex due to its variable clinical course, necessitating advanced imaging and novel biomarkers. genetic profiling, is crucial for personalized treatment. Timely intervention, including the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, hydroxyurea, and kidney transplantation, is essential to mitigate SCN progression.

Search strategy

In this research, an extensive search across databases (PubMed, EMBASE, Scopus, DOAJ) until October 1, 2023, used keywords like “sickle cell disease, Sickle cell nephropathy, chronic kidney disease, dialysis, and transplantation.” Inclusion criteria covered clinical trials, systematic reviews, and retrospective/prospective studies on cancer and hypertension. Non-English studies were excluded. A panel of three authors assessed study abstracts for relevance.

Epidemiology of sickle cell nephropathy

The prevalence of SCN is intricately linked to the global distribution of SCD and SCT(4). According to the study by Naik et al, the incidence of SCN varies across different regions, with a higher prevalence in

populations where SCD and SCT are more common (1). Sub-Saharan Africa, the Middle East, and parts of India exhibit a higher prevalence of SCD and, consequently, SCN (4-6). Additionally, socio-economic factors, access to healthcare, and genetic variations contribute to the diverse epidemiological landscape of SCN (4). Studies suggest that up to 40% of individuals with SCD may experience some form of kidney involvement during their lifetime (7, 8).

The study by Adebayo et al investigates the prevalence of kidney complications in pediatric sickle cell anemia (SCA) patients in the Democratic Republic of Congo and explores the association of clinical and genetic factors with these kidney complications (2). The study enrolled 361 SCA children and measured markers of kidney damage such as albuminuria, hyperfiltration, and decreased estimated glomerular filtration rate (eGFR) (2). The results showed a high burden of kidney damage among Congolese children, with albuminuria, hyperfiltration, and decreased eGFR present in a significant proportion of the patients. Clinical predictors of SCN included frequent blood transfusions, indirect bilirubin, and male gender. They and similar studies also found a significant association between the apolipoprotein L1 (APOL1) high-risk genotype and albuminuria, hyperfiltration, and higher eGFR. Additionally, the haem oxygenase-1 (HMOX1) GT-dinucleotide long repeats were significantly associated with lower eGFR (2,9,10). The study highlights the importance of considering both clinical and genetic factors in understanding and managing kidney complications in pediatric SCA patients (9,10). Kidney disease was found to be highly prevalent in children with sickle cell anemia, with age, hypertension, blood transfusions, and genetic factors identified as the main determinants of SCN (2,7). Moreover, Belisario et al underscore the vulnerability of the pediatric population to SCN, indicating that kidney dysfunction can manifest early in life (11). The age of onset is variable, with some individuals experiencing symptoms in childhood while others may develop SCN in adolescence or adulthood(12). Understanding the age-related dynamics of SCN is crucial for tailoring intervention strategies across the lifespan.

Challenges in diagnosis

Diagnosing SCN presents a significant challenge due to its variable clinical course and the limitations of conventional diagnostic methods. Recently Safdar et al emphasize the complexities of identifying early-stage SCN through traditional approaches like blood and urine tests (13). Microscopic alterations in kidney function frequently go unnoticed, contributing to delayed diagnoses. Furthermore, multiple recent studies underscores the importance of incorporating advanced ultrasound imaging techniques in SCN diagnosis, providing valuable insights into subtle renal changes that conventional methods might overlook (14,15). This additional study accentuates the need for a comprehensive diagnostic approach in addressing the challenges posed by SCN.

Advanced biomarkers for early detection

Recent advancements in biomarker research offer hope for early detection and intervention. Belisario AR et al advocate for the use of novel biomarkers, such as kidney injury molecule-1 (KIM-1) and monocyte chemoattractant protein-1 (MCP-1). KIM-1 is expressed in response to kidney injury, providing a sensitive indicator of early-stage SCN. MCP-1, associated with inflammation, has shown promise in predicting the progression of SCN. Incorporating these biomarkers into routine screening protocols can enhance the sensitivity of detection and allow for early intervention (11). The study by Safdar et al focused on identifying and exploring novel biomarkers for the early detection and management of SCN. The document discusses various biomarkers, including KIM-1, MCP-1, N-acetyl-B-D-glucosaminidase, ceruloplasmin, orosomucoid, nephrin, and cation channels, among others (13). These biomarkers have shown potential for refining diagnostic and therapeutic approaches and may aid in overcoming the limitations of conventional markers of renal damage. The review emphasizes the need for longitudinal studies to validate the efficacy of novel biomarkers and improve the early detection and management of SCN. Additionally, the document highlights the importance of a collaborative approach to standardize and utilize promising new biomarkers and outlines the limitations of conventional markers of renal damage (13).

The role of precision medicine

Given the complexity of SCN's pathophysiology and its diverse clinical manifestations, a precision medicine approach becomes imperative. Recent studies emphasize the need to identify at-risk patients through comprehensive genetic profiling. Genetic factors play a crucial role in SCN, and a deeper understanding of the genetic markers associated with its development can aid in risk stratification (2,11,16).

The findings of the study by Naik et al on-sickle hemoglobin-related nephropathy highlight the major demographic and genetic modifiers of renal disease in sickling hemoglobinopathies. Additionally, they discuss the modifiers of renal disease in SCD, such as α-thalassemia, hemoglobin F, APOL1, and HMOX1, and the potential for a precision medicine approach to risk-stratify patients who may benefit from early intervention (2,11).

Precision medicine allows for targeted therapies, early interventions, and personalized treatment plans, optimizing outcomes for individuals with SCN. Tailoring interventions based on an individual's genetic profile can improve the efficacy of treatments, reduce adverse effects, and slow the progression of SCN (2,11). Collaborative efforts in precision medicine research will pave the way

for more effective and individualized approaches to manage SCN.

Clinical manifestations, progression, and treatment strategies

Understanding the clinical manifestations of SCN is crucial for timely intervention and management. Reentry, Payán-Pernía et al and other studies describe the multifaceted nature of SCN, including microscopic and macroscopic hematuria, proteinuria, and an increased risk of hypertension (12, 17). Hematuria, often a result of microvascular occlusion in the renal medulla, serves as an early indicator of kidney dysfunction (12,17). Proteinuria, indicative of glomerular damage, is a common feature, and its severity correlates with the progression of SCN (12).

According to the study by Sharpe et al, SCN can lead to progressive renal dysfunction, with the need for renal replacement therapy (RRT) becoming necessary when the glomerular filtration rate (GFR) falls below 40 mL/min (12).

Genetic modifiers, such as co-inheritance of alpha-thalassemia, have reduced intracellular HbS concentration and hemolysis, delaying the onset of microalbuminuria in SCD patients (18). Several studies indicate the potential use of hydroxyurea to prevent chronic organ damage in young children with sickle cell anemia (19-21).

The administration of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) is recommended for patients with a urinary protein/creatinine ratio persistently above 100 mg/micromole, as it may reduce the urine albumin and systolic blood pressure and frequency of nighttime urination (12,22). Kidney transplantation appears to offer the best outcome for patients with end-stage renal disease secondary to SCN, with studies showing improved survival rates post-transplantation (12,23,4). According to Bae et al patients with SCD–associated kidney failure exhibited similar decreases in mortality associated with kidney transplantation as compared with those with other kidney failure etiologies (23). As SCN progresses, the risk of developing CKD and kidney failure rises, underscoring the importance of early diagnosis and intervention to mitigate long-term complications. Hypertension is a common comorbidity in SCN, further exacerbating renal damage and increasing the risk of cardiovascular events (25).

Conclusion

In conclusion, SCN presents a significant health challenge, particularly affecting the pediatric population and progressing to CKD and kidney failure in adulthood. The prevalence of SCN is closely tied to the global distribution of SCD and SCT, with higher incidences in regions where these conditions are more common. Adebayo and colleagues' study in the Democratic Republic of Congo revealed a substantial burden of kidney damage in pediatric SCD patients, emphasizing the importance of considering both clinical and genetic factors in understanding and managing SCN.

Diagnosing SCN remains challenging due to its variable clinical course, emphasizing the need for advanced imaging techniques and novel biomarkers. Promising biomarkers such as KIM-1 and MCP-1 show potential for early detection and intervention, addressing the limitations of conventional diagnostic methods. Precision medicine, focusing on genetic profiling, emerges as a crucial approach for risk stratification and personalized treatment plans.

The multifaceted clinical manifestations of SCN, including hematuria, proteinuria, and hypertension, underscore the importance of timely intervention. Treatment strategies involve the use of ACE inhibitors or ARBs, hydroxyurea for preventing chronic organ damage, and kidney transplantation for end-stage renal disease. Early diagnosis and intervention are critical to mitigate the progression of SCN and its associated complications, emphasizing the need for collaborative efforts in research and precision medicine to improve outcomes for individuals with SCN.

Authors' contribution

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Conflicts of Interest

The authors declare no conflict of interest related to the subject matter or materials discussed in this article.

Ethical issues

The research was conducted in accordance with the principles of the Declaration of Helsinki. The authors have observed ethical issues, including plagiarism, data fabrication, and double publication.

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