Overview of Nephrotic Syndrome in Arab Children: Systematic review

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ABSTRACT

Background: Nephrotic syndrome (NS) is a well-documented prevalent chronic condition in childhood. Children afflicted by this ailment often exhibit periorbital swelling, sometimes accompanied by generalized edema. The annual incidence rate of NS in children below 16 years old is estimated to range between 2 and 7 new cases per 100,000 children/year, with a prevalence rate of 0.016%. **Objectives:** This systematic review provides a thorough examination of recent publications regarding the incidence and presentation of nephrotic syndrome in infants and children.

Methodology: We conducted a systematic search for relevant literature in PubMed, SCOPUS, Web of Science, Science Direct, and Google Scholar. Rayyan Qatar Computing Research Institute (QCRI) was utilized to manage the comprehensive selection process. **Results:** Our review encompassed nine studies involving a total of 1,418 patients. The incidence rates, average age, gender distribution within different sample groups, and histopathological patterns exhibited variations influenced by several factors. **Conclusion:** It is concerning to note that children under the age of 17 are at risk of developing a wide range of renal diseases, with nephrotic syndrome being particularly prevalent and severe.

Keyword: Nephrotic syndrome; Incidence; infants; children; Systematic review.

Introduction

Nephrotic syndrome (NS) is defined as a clinical condition characterized by substantial proteinuria, leading to hypo-albuminemia, causing hyperlipidemia, edema, and several associated complications [1]. This syndrome arises from rising permeability in the impaired basement membrane of the renal glomerulus, often due to factors such as infections or thrombo-embolic events [1]. In children, It is typically defined by the excretion < 40 mg/m2/hr of protein, accounting for variations in body size during childhood. In both adults and children, nephrotic-range proteinuria is generally indicated when the-first-morning urine protein/creatinine ratio is 2-3 mg/mg or higher [1, 2]. Abnormal glomerular permeability, the cause of nephrotic syndrome, may be attributed to a variety of conditions, including

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Congenital infections, diabetes, systemic lupus erythematosus (SLE), neoplasia, and the use of certain medications [1, 2]. It can also originate from intrinsic renal disorders. People of various ages may be impacted by this illness. Facial edema is often the first sign of nephrotic syndrome in youngsters. Congenital nephrotic syndrome (birth to 3 months), infantile nephrotic syndrome (from 3 to 12 months), and childhood nephrotic syndrome (age > 12 months) are the three age groups at which symptoms initially manifest [2]. Nephrotic syndrome can develop in children of varying ages; however, it is more frequently observed in children ages from 2 to 7, with a higher prevalence among boys [3]. The most frequent symptom of nephrotic syndrome in children is periorbital swelling [4]. This swelling is typically more pronounced in the early morning and, in mild cases, might be mistaken for seasonal allergies. In children, nephrotic syndrome is categorized into primary nephrotic syndrome, and secondary nephrotic syndrome [4]. Primary nephrotic syndrome in children can be attributed to four types of kidney diseases. These include [5]:

1. The most common cause of nephrotic syndrome in young infants is minimal change disease (MCD).

2. Focal segmental glomerulosclerosis (FSGS), a condition that can lead to scarring in certain glomeruli of the kidneys.

3. Membranous nephropathy (MN), an autoimmune disorder that results in the accumulation of immune proteins in the kidney's glomerular basement membrane.

4. Mesangial proliferative glomerulonephritis.

Secondary nephrotic syndrome in children is often associated with systemic diseases that affect multiple organs or the entire body [6]. Henoch-Schönlein purpura, or IgA vasculitis, lupus, and diseases including hepatitis B, hepatitis C, HIV, and malaria are a few examples. Moreover, particular pharmaceuticals anti-inflammatory like nonsteroidal drugs. medications for mental disorders, bone health, or cancer therapy, and certain blood diseases including leukemia, lymphoma, and sickle cell disease might also be contributing factors [6]. The diagnosis of nephrotic syndrome in children involves a comprehensive assessment, including a review of their medical history and family history, a physical examination, urine tests to detect elevated levels of proteins, and blood tests to evaluate kidney function and identify underlying conditions [6, 7]. In some instances, further diagnostic testing could be necessary to identify the underlying etiology of nephrotic syndrome. These might involve a kidney biopsy, an ultrasound evaluation of the kidneys, or genetic testing [7]. It's crucial to remember that many kids with nephrotic syndrome may not need a kidney biopsy

since they are usually saved for patients who are 12 years of age or older, have complicated medical issues, or have reduced kidney function [8]. The specific treatment for nephrotic syndrome depends on its underlying cause, and as a result, management strategies differ between adult and pediatric populations. In cases of idiopathic nephrotic syndrome in infants or children, corticosteroids are commonly the primary choice. Alternative immunosuppressive medications are usually needed for children with steroid-dependent nephrotic syndrome or those who relapse regularly [7]. Rituximab, an anti-B cell antibody, has shown promise as a non-steroidal substitute for the treatment of juvenile nephrotic syndrome. However, in some children who are dependent on both steroids and calcineurin inhibitors, rituximab may not result in a drug-free remission. For kids with steroid-resistant illnesses, rituximab may also be taken into consideration [8, 9].

Methods

Our systematic review was conceded following established guidelines in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [10].

Study Design: It is a systematic review.

Search strategy: We made a comprehensive search across five major databases, which included PubMed, SCOPUS, Science Direct, Web of Science, and Google Scholar, to identify relevant literature. Our search was limited to English language publications, and we adhered to each database's specific criteria. We transformed the following keywords into PubMed Mesh terms and utilized them to retrieve relevant studies: "nephrotic syndrome", "infants", "Incidence", "prevalence", and "Diagnosis". We employed Boolean operators "OR" and "AND" to combine these keywords as needed.

Selection criteria: We included studies in this review based on the following criteria:

• Randomized control trials (RCTs) and case-control studies that investigated the diagnosis and management approaches for nephrotic syndrome in infants and children.

• Study participants were limited to infants and children (<18 years).

• Only studies conducted in the past twenty years (2004-2023) were considered.

• The study subjects were exclusively humans.

• The articles had to be published in the English language.

• We included only articles that were freely accessible. Data extraction: Rayyan Qatar Computing Research Institute (QCRI) was used to verify for duplication in the output of search strategy [11]. Using a set of inclusion and exclusion criteria, the researchers adjusted the collective search results to assess the relevance of the abstracts and titles. Every paper that fulfilled the inclusion criteria was thoroughly scrutinized by the researchers. The writers discussed conflict resolution strategies. The approved study was uploaded using a previously made data extraction form. Data on study titles, year of study, authors, nation, gender, participants, purpose of study, and primary outcomes were extracted by the authors. The risk of bias evaluation was made on a different page. Strategy for data synthesis: Summaries of the findings

strategy for data synthesis: Summaries of the findings and study components were created using data from pertinent research, providing a qualitative overview of the findings. After the data for the systematic review were acquired, the most efficient technique for using the data from the included research articles was chosen.

Results

Search results: The systematic search produced 512 study articles in total, of them 77 duplicates were eliminated. After, 435 of the studies underwent title/abstract screening, 390 research were deemed ineligible for inclusion. No articles were found after 45 reports were requested to be retrieved. Forty-five papers were ultimately reviewed for full-text assessment; 24 were disqualified due to wrong study outcomes, 12 due to incorrect population type, and 4 were correspondence with the editors. This systematic review contained five eligible study papers. (Figure 1) presents a synopsis of the research selection procedure.

Included studies characteristics: The sociodemographic details of the research articles that are included are shown in (Table 1). There were five trials totaling 1,418 people in our data. Retrospective studies comprised five papers [12-16]. The objectives and findings of the included researches are shown in (Table 2).

Discussion

Massive proteinuria and edema are characteristics of the frequent pediatric glomerular illness known as nephrotic syndrome. Chronic renal disease, complications from the condition, and adverse effects from therapy are all possible risks. The majority of instances of nephrotic syndrome are of the main idiopathic variety, which often develops after an apparent benign illness in early infancy. Although there are other choices for treatment, corticosteroid medication is the conventional course of action for many weeks [17, 18]. The prevalence of nephrotic syndrome exhibits variability across several demographic cohorts and is shown to range from 0.002% to 0.007% of children [19]. Multiple studies have shown variations in the rate of occurrence, average age of initiation, and gender distribution [18]. A study conducted by Kaddah et al. [12] revealed a

higher prevalence of males (74%) and a mean age of illness of 4.43 ± 2.7 years. Additionally, it was observed that 81% of patients experienced the onset of the condition at or before the age of 6 years. In previous investigations, the average age at which symptoms first appeared varied between 4.6 and 5.4 years. Additionally, the proportion of individuals who had symptoms at or before the age of 6 ranges from 46% to 79% [12]. A separate investigation revealed a near-equivalent distribution of males and females among pediatric patients diagnosed with nephrotic syndrome [12]. Studies have reported a wide variation in the epidemiology of nephrotic syndrome among infants and children due to various causes [20]. For instance, Mubarak et al. [17] found that minimal change disease (MCD) and its variants accounted for 43.8% of cases, with MCD being the most prevalent subtype [20, 21]. This was consistent with findings from studies in the USA and India. Patients with nephrotic syndrome lose significant protein in their urine, causing hypoproteinemia and subsequent edema, along with associated hypercholesterolemia, hyperlipidemia, and higher lipiduria [22, 23]. The incidence of hypertension and microscopic hematuria among children in India was 41% and 26.8%, respectively. Different studies reported varying histopathological patterns, with focal segmental glomerulosclerosis (FSGS) being the most frequent subtype in some, while minimal change disease was predominant in others [24, 25]. Studies also reported differences in the prevalence of FSGS, ranging from 15% to 59% [26, 27]. FSGS was consistently reported as the primary underlying histopathology in children with SRNS in various studies [28]. Furthermore, the clinical indications for renal biopsies in different studies varied. Nephrotic syndrome was the most common indication in some, while SLE, nephritic syndrome, and other indications were reported in others. This variability concurs with previously published data internationally [28, 29]. Primary glomerular diseases, particularly the primary ones, were found to be the most common pediatric renal diseases, accounting for 75.6% of all renal diseases. This finding aligns with previously published data from Iran and other countries, which also observed primary glomerular diseases as the predominant entity [30]. However, reports from other countries have identified different entities, such as hereditary nephropathies and congenital urologic malformations, as the most common causes [30, 31]. There have been documented instances of disparities in the response of steroids and the progression of diseases, with geographic location and ethnic background being key factors. In the past, sub-Saharan Africa has documented elevated levels of steroid resistance [8]. However, research indicates a growing prevalence of



Identification of studies via databases and registers

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart summarizes the study selection process.

Study	Study design	Setting	Participants	Mean age (years)	Males No. (%)
Alharthi, 2017 [12]	Retrospective	Taif region	87	5.8	45 (51.7%)
		Aljouf, Saudi			
Alhassan, et al., 2013 [13]	Retrospective	Arabia	25	6.2	17 (68%)
		western Saudi			
Abdullah, 2012 [14]	Retrospective	Arabia	242	29.7 ± 13.1	122 (50.4%)
		Jeddah, Saudi			
Kari et al., 2009 [15]	Retrospective	Arabia	36	4.3 ± 3.0	11 (30.5%)
Kaddah et al., 2012 [16]	Retrospective	Egypt	100	9.84 ± 3.9	74 (74%)

 Table 1: Some demographic characteristics of the included participants.

Table 2: Clinical characteristics and outcomes of the included studies.

Study	Aim	Main outcomes	ROBIN- I
Alharthi, 2017 [12]	To document the clinical characteristics, various histopathological patterns of nephrotic syndrome (NS) in pediatric patients, and their responses to treatment.	This study revealed a steroid therapy responsiveness rate of 70%, which closely aligns with findings in several other studies. A substantial portion of patients with steroid-sensitive nephrotic syndrome exhibited steroid dependence (30%), while 17% experienced frequent relapses. The major histological patterns observed in childhood steroid-resistant nephrotic syndrome (SRNS) cases were focal segmental glomerulosclerosis (FSGS), membranoproliferative glomerulonephritis, and minimal change disease (MCD) nephropathy. The heightened occurrence of SRNS and steroid-dependent nephrotic syndrome among our patients could be attributed to the high rate of consanguinity.	High
Alhassan, et al., 2013 [13]	To ascertain the incidence and prevalence of various NS patterns in children and assess their responses to therapy.	The NS patterns and treatment responses observed in this study were consistent with findings in studies conducted worldwide.	Moderate
Abdullah, 2012 [14]	To evaluate the distribution and prevalence of all histopathological categories of renal diseases in the pediatric age group, spanning from birth to 17 years of age, within a prominent academic center.	The incidence of different nephropathies, particularly glomerulopathies, in the pediatric age group varies not only within our country but also across different countries due to the factors mentioned earlier. In this study, nephrotic syndrome serves as the most prevalent clinical indication for renal tissue sampling, with glomerulonephritis being the most frequently identified pathology.	Moderate
Kari et al., 2009 [15]	To provide a report on the histopathological patterns of SRNS in children presenting at King	FSGS was the most prevalent underlying histopathology observed in children who presented with SRNS at our institution. A few other children had underlying causes such as	High

	Abdul Aziz University Hospital	IgM nephropathy and various forms of MCD, including	
	(KAUH)	MesPGN and CIqNP.	
	To conduct an analysis of the		
	epidemiological, clinical, and	We observed a higher proportion of steroid-resistant patients	
	histopathological characteristics in	among our study participants in comparison to findings in other	
	Egyptian children diagnosed with	studies. The response to immunosuppressive treatment varied	Moderate
	idiopathic NS and document their	from what has been reported in other studies, possibly attributed	
Kaddah et	responses to various treatment	to differences in the selection criteria for initiating	
al., 2012 [16]	modalities.	immunosuppressive therapy.	

Steroid-sensitive individuals in this region [2]. Previous research has shown a range of corticosteroid sensitivity, with reported percentages being between 76% and 87% [29]. In previous studies, steroid resistance occurred in 34% of cases after initial prednisone therapy, higher than rates observed in most other studies, where steroid resistance ranged from 9.4% to 22% [16, 29]. Early detection and proper management of Nephrotic Syndrome (NS) are essential to prevent further kidney damage and complications. This includes regular monitoring of kidney function, blood pressure, and cholesterol levels, as well as the use of medications to control proteinuria and reduce swelling [32]. In some cases, children with NS may require immunosuppressive therapy or other interventions to help manage their condition [32]. Furthermore, it is important for healthcare professionals to consider the cultural and social factors that may impact the care of Arab children with Nephrotic Syndrome [33]. This includes understanding the family's beliefs and practices related to healthcare, as well as addressing any barriers to accessing care and treatment [33]. By understanding the unique factors that contribute to the prevalence of this condition in this population, healthcare professionals can provide better support and improve outcomes for affected children. It is essential for healthcare professionals to stay informed about the latest research and guidelines for managing Nephrotic Syndrome in Arab children, and to work collaboratively with families and other healthcare providers to ensure the best possible care for these vulnerable patients [16].

Conclusion

It is concerning to note that children under the age of 17 are at risk of developing a wide range of renal diseases, with nephrotic syndrome being particularly prevalent and severe. The prevalence of these diseases varies across different countries due to socioeconomic, geographical, and genetic factors. It is important to consider these differences in order to better understand and address the patterns and development of these conditions. Additionally, the observed variations in disease incidence, treatment responses, and histopathological findings highlight the need for further research and tailored approaches to pediatric renal diseases.

Conflict of Interest

None

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None

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