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NEPHROTIC SYNDROME OVERVIEW

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Abstract:

Introduction: *Nephrotic syndrome (NS) is considered a very common kidney illness that affect children. It is known by leaking of proteins from the blood to the urine by the damaged glomeruli. It is traditionally defined by nephrotic-range proteinuria (more than forty mg/ m2/hour or urine protein/creatinine ratio more than 200 mg/mL or 3 + protein on urine dipstick), hypoalbuminaemia (less than 25 g/L) and edema [1]. Children affected by NS can be congenital. It usually present within the first three months of life, and in these pediatric population there is often a genetic mutation affecting either the podocyte or the glomerular basement membrane, though it rarely could be linked with congenital infections, like cytomegalovirus. Apart from the congenital form of nephrotic syndrome, many causes could lead to nephrotic syndrome, involving glomerular disorders, vasculitides, infections, toxins, malignancy, genetic mutations and, most importantly, unknown.*

Aim of work: *In this review, we will discuss nephrotic syndrome.*

Methodology: *We did a systematic search for nephrotic syndrome using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.*

Conclusions: *Generally speaking, the prognosis for NS is considered very good, with less than five percent that develop rapidly progressing to end-stage renal disease. As mentioned, steroid resistance continues to be the most important risk factor for future development of CKD. Though there are significant adverse effects from chronic use of steroids and steroid-sparing medications, the current management plan are successful in putting the patient into remission across the spectrum of the illness. There continue to be a lot of unanswered questions, including (1) who develop NS and the etiology, (2) what could explain the individual variability in response to different management plan, and (3) what are the specific risk factors that lead to relapse. More research is required to study the causes and duration guideline for calcineurin inhibitors, mycophenolate mofetil and rituximab therapies. Finally, we need to develop new therapies for the management of steroid-resistant disease. Further work is needed to close the gaps in our understanding of the different causes and the diversity of the clinical course of this common and complex childhood disease.*

Key words: *nephrotic syndrome, children, presentation, causes, management.*

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INTRODUCTION:

Nephrotic syndrome (NS) is considered a very common kidney illness that affect children. It is known by leaking of proteins from the blood to the urine by the damaged glomeruli. It is traditionally defined by nephrotic-range proteinuria (more than forty mg/ m2/hour or urine protein/creatinine ratio more than 200 mg/mL or 3 + protein on urine dipstick), hypoalbuminaemia (less than 25 g/L) and edema [1]. Children affected by NS can be congenital. It usually presents within the first three months of life, and in these pediatric population there is often a genetic mutation affecting either the podocyte or the glomerular basement membrane, though it rarely could be linked with congenital infections, like cytomegalovirus. Apart from the congenital form of nephrotic syndrome, many causes could lead to nephrotic syndrome, involving glomerular disorders, vasculitides, infections, toxins, malignancy, genetic mutations and, most importantly, unknown.

In this review, we will discuss the most recent evidence regarding nephrotic syndrome

METHODOLOGY:

We did a systematic search for nephrotic syndrome using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: nephrotic syndrome, children, presentation, causes, management.

OVERVIEW:

Classically, the histological classifications could be corresponding with idiopathic childhood NS are known as either minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGS) — the quintessential podocyte diseases, or podocytopathies [2]. MCD is considered more common in childhood NS than FSGS and known by to glomeruli which appear normal on light microscopy with evidence of podocyte foot process effacement by electron microscopy. FSGS has a likewise morphology on electron microscopy, however, dissimilar to MCD, on light microscopy shows segmental destruction of the glomerular capillaries with adhesions/synechiae forming between the sclerosed segments and Bowman's capsule. Insults to these foot processes lead to a change in podocyte morphology and rearrangement of their cellular cytoskeleton, which leads to loss of serum protein through the glomerulus [3]. This modification in shape could often be reversed with corticosteroid therapy in MCD, however is usually resistant and progressive in the setting of FSGS. Recently, MCD and FSGS are considered histological definitions within a wide range of illnesses, with MCD demonstrating an earlier stage that is responsive to treatment and FSGS considered an advanced and resistant stage of the disease [4].

Idiopathic NS is clinically categorized based on response to corticosteroid therapy. Between eighty percent and ninety percent of children over one year of age presenting with NS respond to treatment with steroids within four weeks [steroid-sensitive nephrotic syndrome (SSNS)], whereas the remaining ten to twenty percent are non-responsive and categorized as having steroid-resistant nephrotic syndrome (SRNS) [5]. In kids with SSNS, the subsequent course of illness could vary widely, with the majority of kids having at least 1 episode of relapse, and up to fifty percent having either frequently relapsing nephrotic syndrome (FRNS) (more than two relapses in first six months or more than four relapses in any one-year period) or steroid-dependent nephrotic syndrome (SDNS). Noteworthy to mention is that South Asian and South-east Asian children have significant lower odds of FRNS than European children. SRNS is more likely to be linked to FSGS histology, and has higher likelihood of progressing to end-stage renal disease (ESRD) [6]. In kids with SSNS, though very rare, relapses may continue beyond adolescence into adulthood, with the number of relapses in childhood and administration of steroid-sparing medication, such as cyclophosphamide, calcineurin inhibitors (CNIs) or rituximab, being the two most important risk factors [7].

Epidemiology

The incidence of childhood NS is calculated as four (ranging between 1.15–16.9) per 100,000 children globally, with a significant variability based on ethnic background and the location [8]. In many European studies, South Asian children were found to have a higher incidence of NS than the European population [9], and historical data from USA studies shows a higher incidence in African-American children than in children of European decent. African-American kids also have an higher likelihood of having FSGS on kidney biopsy and overall are more likely to progress to ESRD than European children [10]. Likelihood of having SRNS also varies by ethnicity and geographical location, with twenty percent reported in Europeans, fifteen percent in Africans, thirty percent in Asians and thirty percent in South

Asians [11]. Most of these studies are retrospective or cross-sectional, but, true causative factors explaining these differences in steroid response cannot be determined.

Etiology

In one of the recent prospective, longitudinal, multicentre study in the USA of children and adults (NEPTUNE, Nephrotic Syndrome Study Network), the causes of NS were as follows:

Pathophysiology

Podocyte and glomerular filtration barrier defects

Podocytes are very differentiated cells that support and maintain the kidney's glomerular basement membrane filtration mechanism. These cells are comprised of a cell body that expands many foot processes that wrap around glomerular capillaries. Foot processes connect with special cell–cell junctions called the slit diaphragm which together form the glomerular filter. A complex cytoskeleton maintains the structure of the podocyte cell body and foot processes to let modifications in hydrostatic pressures in response to different molecular movement across the glomerular membrane.

Podocytes cells have very limited ability to divide and regenerate and are therefore vulnerable to injury [12]. Damages of podocytes above a critical mass can lead to irreversible glomerular damage, with podocyte depletion of more than twenty percent lead to progress of glomerulosclerosis and progressive loss of kidney function [13].

Genetic mutations in podocyte structure and function lead to kidney dysfunction, presenting often as either congenital or SRNS. One earliest recognized genetic disorders engaged genes encoding slit diaphragm proteins nephrin (NPHS1) and podocin (NPHS2) [14]. Mutations in genes encoding the podocyte actin cytoskeleton, including CD2AP and INF2, are also linked with SRNS phenotypes.

Immune dysregulation

Immunosuppression with corticosteroids is considered the main way treatment of nephrotic syndrome, it is very logic to suspect immune dysregulation plays a pathogenic role in disease development. Moreover, there is evidence that Hodgkins and other T-cell lymphomas can lead to nephrotic syndrome, and chemotherapy could subsequently lead to remission. Measles infection can also lead to a temporary spontaneous remission in NS by depression of cell-mediated immunity and T-cell subsets. Though there's no specific cytokine can lead to nephrotic syndrome, clinical patterns of disease occurrence certainly suggest that there is a role for T-cell dysregulation in the pathophysiology of disease.

Systemic circulating factors

Circulating permeability factors may also play a role in the pathogenesis of nephrotic syndrome, as evidenced by the recurrence of proteinuria after renal transplantation in the setting of FSGS, and with induced remission of FSGS after plasma exchange, particularly in the early post-transplant period [15]. Furthermore, serum from patients with FSGS has induced proteinuria in rat kidneys and increased glomerular permeability to albumin *ex vivo*, FSGS has been transmitted from mother to child [16], and implantation of a kidney with FSGS into a recipient without the disease has induced remission.

Clinical features

The typical presenting symptom in NS is edema, with periorbital, labial/scrotal and lower extremity swelling. In severe clinical situations, anasarca could also develop, leading to ascites and pleural/pericardial effusions. This could also lead to abdominal pain from hypoperfusion and ileus, dyspnea and cool extremities. Presence of abdominal pain can also lead to further investigation to rule out spontaneous bacterial peritonitis. Generally, kids with NS are at high risk of serious bacterial infections, like peritonitis, sepsis and pneumonia owing to T-cell dysfunction and loss of immunoglobulins in the urine. Infection is the main cause of morbidity, and, mortality in children with NS.

Oliguria and intravascular volume depletion could also develop, leading to acute kidney injury (AKI), another important complication of nephrotic syndrome. It is well known that NS is a hyper-coagulable state with a risk of developing deep vein thrombosis (DVT), cerebral sinus venous thrombosis, pulmonary embolism, renal vein thrombosis and, more rarely, arterial thromboses [17].

Edema in nephrotic syndrome

There are 2 hypotheses that have been suggested for the etiology of edema in nephrotic syndrome: the underfill and the overfill hypotheses. Neither hypothesis can fully explain the pathophysiology of edema in NS as there is probably some overlap of children presenting intravascularly volume depleted and 'under-filled', euvolemic, or volume overloaded and over-filled.

The underfill hypothesis suggests that high-grade proteinuria results in hypoalbuminaemia that can decrease plasma oncotic pressure, leading to fluid leakage into the interstitium. As a result, the intravascular volume depletion, tachycardia,

hypotension and oliguria can develop and the renin-angiotensin aldosterone system (RAAS) becomes activated. Not all clinical circumstances fit this hypothesis, but, as albumin replacement alone is often insufficient to stimulate diuresis without the addition of a diuretic. Some children respond to diuretic medication alone without albumin [67], and, as they enter remission, most will experience a diuresis well before normalisation of serum albumin level.

Opposite to the overfill hypothesis suggests that protein loss in the urine leads to consequent sodium retention, thereby causing intravascular volume expansion, leading to fluid overflow into the interstitium. Recent studies have also suggested that there may be a commonality in pathophysiology between the hypoalbuminaemic states in childhood NS and oedematous malnutrition, such as kwashiorkor [18]. There are controversial views of the use of intravenous albumin in the setting of kwashiorkor to correct serum oncotic pressure, so mobilising fluid and correcting the oedema.

Diagnostic investigations

Assessment of NS at first presentation must include the following baseline investigations: (i) urinalysis and urine microscopy, (ii) quantified protein:creatinine ratio on a spot sample or on 24 h collection, and (iii) serum electrolytes, albumin, renal function, complete blood count and cholesterol. If there is any suspicion of a combined nephritic picture, a more targeted investigations might also include serum complement levels (C3 and C4), antinuclear antigen (ANA), anti-double stranded DNA (anti-dsDNA).

Genetic testing must be considered in the following situations: congenital nephrotic syndrome, SRNS, family history of NS or if there are clinical features of syndromic disease. Renal biopsy is usually not required at diagnosis.

MANAGEMENT:

Corticosteroids

The mainstay therapy for NS is oral corticosteroids which, were found to dramatically decrease mortality (to three percent) and lead to remission in about eighty percent of children with NS. Corticosteroids are believed to work by many mechanisms, but overall their specific action is not fully understood. The main effect is through regulation of cytokine gene expression through the glucocorticoid receptor, acting to induce genes coding for anti-inflammatory cytokines and suppress genes for pro-inflammatory cytokines. Recently, corticosteroids are reported to suppress T-cell function, and to stabilize the podocyte cytoskeleton.

Adverse effects of corticosteroid therapy in children with NS include growth impairment, development of cataracts and substantial weight gain. Additionally, behavioural and psychological adverse effects are not uncommon, including anxiety, depression and aggressive behavior [19]. Given that they often require multiple courses throughout their lifetime, children with often relapsing and steroid-dependent NS are at higher risk of these side effects.

Cyclophosphamide

Cyclophosphamide is one of the most commonly used steroid- sparing agent globally and has been effective in multiple RCTs for the management of frequently relapsing NS. Though used in SDNS, cyclophosphamide has been shown more recently to produce less favorable results in this setting.

Levamisole

Levamisole is immunomodulatory agent that is prescribed to spare therapy with steroids in the setting of SDNS and FRNS. It is also used as an antihelminthic agent, it is thought to act by augmenting the type 1 immune response while down-regulating the type 2 response by inducing transcription of the cytokine, interleukin-18. Though, in comparison to placebo, it might decrease the risk of relapse, the data are limited and there has been no conclusion. Levamisole has a more bearable side-effect profile than cyclophosphamide.

CNIs

Both cyclosporine and tacrolimus are considered effective in the management of FRNS and SDNS, though no clinical studies have compared the two CNIs. Most of the evidence available has showed the efficacy of cyclosporine; but, due to the significant cosmetic adverse effects of hypertrichosis and gum hyperplasia, tacrolimus is being used increasingly. Both medications could lead to hypertension, renal dysfunction and have a potential for diabetes mellitus which are often dose-related [20].

Mycophenolate mofetil

Mycophenolate mofetil (MMF) has inhibitory effects on T and B lymphocytes and cytokine gene expression treatment with MMF is usually used in FRNS or SDNS to spare the more significant adverse-effects of both calcineurin inhibitors and cyclophosphamide. Regarding the efficacy, MMF has been less well than cyclosporine in preventing relapse in patients with FRNS; but, the nephrotoxic adverse

effects of CNIs are spared. Recently, it was proposed that higher levels of mycophenolic acid (the active form of the drug).

Rituximab

Rituximab, a monoclonal antibody that binds to the CD20 antigen on B-cells, is a newer therapeutic agent for more advanced SSNS. Studies have shown that it induces remission in FRNS and SDNS; however, there is no benefit in using it for SRNS. 2 RCTs showed the short-term (less than one year) safety of rituximab; they also showed that rituximab combined with lower doses of corticosteroid and calcineurin inhibitors was not inferior to standard therapy in maintaining remission in FRNS, and that CNIs and steroids could be weaned off with remission continued.

Further work is needed to close the gaps in our understanding of the different causes and the diversity of the clinical course of this common and complex childhood disease.

CONCLUSIONS:

Generally speaking, the prognosis for NS is considered very good, with less than five percent that develop rapidly progressing to end-stage renal disease. As mentioned, steroid resistance continues to be the most important risk factor for future development of CKD. Though there are significant adverse effects from chronic use of steroids and steroid-sparing medications, the current management plan are successful in putting the patient into remission across the spectrum of the illness. There continue to be a lot of unanswered questions, including (1) who develop NS and the etiology, (2) what could explain the individual variability in response to different management plan, and (3) what are the specific risk factors that lead to relapse. More research is required to study the causes and duration guideline for calcineurin inhibitors, mycophenolate mofetil and rituximab therapies. Finally, we need to develop new therapies for the management of steroid-resistant disease. Further work is needed to close the gaps in our understanding of the different causes and the diversity of the clinical course of this common and complex childhood disease.

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