UNDERSTANDING FUNCTIONS AND FEATURES OF NEPHROTIC SYNDROME

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ABSTRACT

NS is one of the most common manifestations of glomerular disease, characterized by heavy proteinuria and hypoalbuminemia or hypoproteinemia and its progressive forms can lead to Chronic Kidney Disease (CKD) and/or End-Stage Renal Disease (ESRD). It is caused by increased permeability of serum protein through the damaged basement membrane in the renal glomerulus. Though, the disease has been reported in both children and adults. A keen of the molecular systems of the illness may likewise yield new data about etiology and will be useful in creating focused on treatments against the infection. The outcomes unequivocally show that the changes and SNP of NPHS1, NPHS2 and MDR1 qualities adds to the pathogenesis of NS.

Keywords: Nephrotic Syndrome, disease, Chronic, kidney, infections, etc.

1. INTRODUCTION

NS is one of the most common manifestations of glomerular disease, characterized by heavy proteinuria and hypoalbuminemia or hypoproteinemia and its progressive forms can lead to Chronic Kidney Disease (CKD) and/or End-Stage Renal Disease (ESRD). It is caused by increased permeability of serum protein through the damaged basement membrane in the renal glomerulus. Though, the disease has been reported in both children and adults, it is 15 times more common in children than adults. NS is classified into either primary glomerulopathy, accounting 90% or secondary glomerulopathy, associated with systemic diseases such as HenochSchonleinpurpura, systemic lupus erythematosus, hepatitis B infection, collagen and vascular diseases, encompassing the remaining 10%. Thus, NS is a constellation of renal and extra renal manifestations that can be caused by a multitude of systemic diseases (secondary) as well as by primary insults to the kidney (primary). Primary NS is the most frequent form of NS in children representing more than 90 percent of cases between 1 and 10 years of age and 50 percent after 10 years of age.

During the 20th century attempts were made by several researchers to discriminate nephritis (i.e. kidney disease distinguished by exudation and proliferation) from nephritis (i.e. nephritis). It was noticed that nephritis is not a single disease, but a group of related diseases that causes proteinuria. The word “nephritis” was replaced by “nephritic syndrome” (NS). Clinically NS features develop into rigorous proteinuria, hypoalbuminemia, edema and hyper cholesterol conditions. The electron microscopy information leads to the recognition of negative charged molecules in the GMB, which prevent the passage of anionic macromolecules like albumin.

A. Clinical features of NS

Clinically, NS is characterized by a triad of massive proteinuria (>40 mg/m2 per hour), hypoalbuminaemia (≤ 2.5 mg/dl), hyperlipidaemia (serum cholesterol >200 mg/dl) presence of edema and hypovolemia. Structural and functional abnormalities in the GFB resulting in severe proteinuria are responsible for the clinical manifestation. Alterations on the perm selectivity barrier of the glomerular capillary wall are not able to restrict the loss of protein such as albumin to less than 100 mg/m2 body surface per day. Primarily, intermediate size (60-200 kDa) plasma proteins are lost,
which leads to a marked change in plasma protein composition and resulted into fall of plasma oncotic pressure and rises in viscosity. The changes in plasma protein composition and oncotic pressure determine most of the secondary consequences of NS. The dysfunction of tubular reabsorption causes tubular proteinuria.

The main markers of tubular proteinuria are β2-microglobulin and globulins. If the levels of plasma proteins are increased, they can be filtered in excess of the reabsorption capacity of the tubules and then be present in the urine; this is called overflow proteinuria. Proteinuria is referred to as secretory proteinuria or histuria when the urinary proteins originate from surrounding tissues or other organs via excretion and secretion. The proteinuria in childhood NS is relatively selective, constituted primarily by albumin. In the milder forms of NS, plasma albumin levels are reasonably preserved (>25 g/L) and the plasma volume is expanded. Severe NS is characterized by marked hypoalbuminemia (<20 g/L and can fall below 10 g/L), severe edema and occasionally hypovolemia that is reflected by normal or low blood pressure. In the first few years of life, children with NS often show periorbital swelling with or without generalized edema. Edema is the predominant feature resulting from an imbalance between the hydrostatic and colloidal osmotic pressure in the intravascular and extracellular compartments. As serum albumin falls below 20 g/L, compensatory mechanisms, such as activation of the renin-angiotensin-aldosterone axis with an increased tubular reabsorption of sodium, further increase the formation of edema. Apart from these clinical features, oliguria, abdominal tenderness, fever, hematuria, uremia and thrombosis were found in descending orders in NS patients. Diabetes mellitus and hypertension are risk factors. Some patients may present with complications of NS as their initial manifestation like thromboembolism, septicemia, skin sepsis, infections, peritonitis, malnutrition, anemia, and hypocalcaemia.

B. Classification of NS

Traditionally, NS is classified into primary and secondary subtypes; the former is due to primary glomerular diseases, while the latter is associated with specific etiologic events or a complication of other diseases. On the basis of their etiology, glomerular injury can be divided into either acquired (caused by metabolic toxins or environmental infection) or hereditary (genetics/familial). These two categories may have significant overlap with each other and in some cases, the cause of the disease is less apparent. The disease further classified based on the:

(i) Age of onset

(ii) Histopathology findings and

(iii) Patient’s response to steroid therapy. Classification based on the various criteria has summarized and shown below in Figure 1.
Primary NS is a group of diseases with the typical characteristics of NS, with unknown etiology. They are further categorized based on histopathology.

a. **Histopathological classification:** According to histologic lesions, primary NS are categorized into minimal change nephrotic syndrome (MCNS), focal segmental glomerulosclerosis (FSGS), diffuse mesangial proliferative glomerulonephritis (DMPG) and membranous nephropathy (MN).

b. **Minimal Change Nephrotic Syndrome (MCNS):** MCNS is called as a Nil disease, as no significant lesions are detected in glomeruli (renal) morphology (3, 19). The disease is also called minimal change lesion or minimal change disease (MCD), to stress the relative paucity of glomerular lesions under light microscopy. The glomeruli appear largely normal, with mild increase of cellularity in the mesangial area and enlargement of epithelial cells. Proximal tubules may contain fine lipid droplets.

c. **Focal Segmental Glomerulo Sclerosis (FSGS):** FSGS is characterized by the presence of sclerosis in a part of the glomerular tuft. That is pathological findings revealed the presence of focal and segmental sclerotic lesions or scars, affecting a portion of glomeruli, usually those in the deeper, juxtamedullary cortex due to the higher perfusion pressure. Electron microscopy examination revealed the effacement of podocytes and the detachment of foot processes from the GBM, especially when heavy proteinuria is observed.

These groups of diseases are caused by known etiologies (Table 1.1). Nevertheless, the secondary NS have the similar histologic patterns as to that of the primary NS, though they may exhibit some difference inclusion bodies.

The various drugs used in the management of NS, steroid administration remains the primary option. Steroid responsiveness is the most important prognostic indicator of NS and appears to be the single most important clinical parameter indiffereniating patients of primary NS. Based on response, the patients are classified into either Steroid-Sensitive NephroticSyndrome (SSNS) or Steroid-Resistant NephroticSyndrome (SRNS). The vast majority of patients with primary NS (>90 percent) respond to glucocorticoid therapy and are termed as SSNS.

SRNS is defined as a child with NS who fails to show a complete remission of symptoms after using the full prescribed steroid treatment. About 10–20% of children (<10 years of age) failed to respond to corticosteroids are classified as steroid resistant. The steroid resistance can be grouped into primary
resistance (failure of complete remission after treatment for the first time) and secondary resistance (initially responds well to steroid regimen for a period of time, after which shows recurrence and failure of complete response). FSGS, MPGN and MCD were the morphologic lesions seen in 70%, 44% and 7% of children with SRNS, respectively. The children with SRNS tend to progress to CKD (Stage V)/ESRD due to the progressive damage of the GFB. Molecular studies performed in children with sporadic primary SRNS have identified mutations in several genes encoding proteins involved in maintaining the integrity of GFB. Therefore, mutational analysis in SRNS would help in preventing unnecessary exposure to immunosuppressants and their adverse effects, besides helping in prognostication.

Based on the age of onset it is further classified as (a) congenital (before 3 months of age) (b) infantile (3-12 months) (c) early childhood onset (13 months to 5 years), (d) late childhood onset (6 to 12 years), (e) adolescent onset (13 to 17 years) and (f) adult onset (>18 years) types. Moreover, age of onset may also be predictive of the underlying histologic lesion causing NS. While, the MCNS is seen in 80% of children diagnosed with NS before 6 years of age, it was 18% of those with FSGS and 2% of those with MPGN present for the same age. Within 5 years of diagnosis, 21% of children with FSGS developed ESRD and another 23% developed CKD. Thus in a child diagnosed as having FSGS, the risk of developing CKD or ESRD within 5 years is almost 50%.

2. STRUCTURE AND FUNCTION OF THE KIDNEY

The two kidneys are a pair of bean-shaped organs situated in the retroperitoneal space. The kidney size in an adult human averages 11-12cm in length, 5.0-7.5 cm in width and 2.5-3.0 cm in thickness. The weight of each kidney varies from 125 to 170g in the adult male and 115-155g in an adult female. The kidney is covered by three layers; that is from interior to the exterior: Fibrous capsula, Adipose capsula and Renal fascia. A bisected kidney surface has two distinct regions the outer cortex has glomeruli and proximal tubules; the inner medulla rich in henle loops and collecting ducts. The structural and functional unit of kidney is nephron, each kidney has about one million nephrons. Every nephron consists of one renal corpuscle and its associated tubules. The renal corpuscle is further divided into glomerulus, bowmans capsule and juxtaglomerular apparatus. One glomerulus composed of 5-7 capillary branches originating from the afferent artery, whose surface is extensively covered by glomerular podocytes. The lumen of the glomerular capillary is lined by a thin fenestrated endothelium. Between the podocytes and endothelium is a layer of a mesh-like structure, the glomerular basement membrane (GBM), which prevents leakage of plasma macromolecules.
It is vital for maintaining the stable homeostasis of the human body; regulates body fluid and maintains osmolarity, electrolytes and excretion of wastes such as keratinize urea, and uric acid. Furthermore, the kidney can produce and secrete erythropoietin and then regulate the maturation process of erythrocytes in the bone marrow. It also secretes rennin, stored in juxtaglomerula cells, used to adjust blood volume, blood vessel contraction and promote the secretion of other hormones. The kidney is a vital site for the action of 1, 25-dihydroxyvitamine D3.

One of the kidney’s most important functions is filtration of the blood by glomeruli, allowing excretion of fluid and waste product, while retaining all blood cells and proteins within the blood stream. During glomerular filtration, plasma fluid traverses several cellular and extracellular layers that make up the complex structure of the ultra filtration unit. From inside outward, it consists of endothelial fenestrate, GBM, and epithelial foot processes with intervening slit diaphragms (Figure 1.2). The integrity of each of these structural elements is essential for the maintenance of normal ultra filtration.

3. Treatment and Management

Steroids are the mainstay of therapy for children with NS. The initial therapy for childhood NS comprises oral glucocorticoids (prednisone 60 mg/m2 per day for 4 weeks, with the maximum dosage of 80 mg). This is followed by prednisone 40 mg/m2 on alternate days for 4 weeks, with a steroid taper over 3 to 6 months most patients respond to steroid therapy and a high proportion of them relapses but continues to respond throughout the subsequent course of the disease. To prevent relapses, they were also administered levamisole (2 mg/kg on alternate days). Cyclosporine may be useful in steroid-dependent patients with signs of steroid toxicity and after a failure of a course of alkylation agent. Almost 85% of patients respond to cyclosporine, but they relapse after tapering or stopping the drug. In SRNS patients, there is no study showing a clear-cut beneficial effect of alkylation agents, as the remission rate after treatment is close to the rate of spontaneous remission. Cyclosporine in association with prednisone may be effective, but the risk of nephrotoxicity seems to be higher than in steroid dependent patients.
Roughly 95% of patients with MCNS and 20% with FSGS achieve remission after an 8-week course of prednisone (60 mg/m² daily for 4 weeks followed by 40 mg/m² on alternate days for 4 weeks). Traditionally, patients receive divided doses but once-daily treatment also seems to be effective and majority of those patients (75%) respond within 2 weeks. Given the high relapse rate for MCNS patients, there has been a shift in the past decade to longer courses of corticosteroid treatment for first episodes of NS in an effort to decrease the relapse rate. A mainstay of therapy in steroid-resistant FSGS is the use of ACE inhibitors, which reduce proteinuria and the rate of decline in glomerular filtration rate (GFR) in a variety of forms of glomerular disease. Another therapeutic agent is mycophenolate mofetil, which in sporadic reports and open-label trials resulted in relapse in <50% of patients. Non-steroidal anti-inflammatory agents also have been used, usually in association with ACE inhibitors. This therapeutic approach, although sometimes reduces proteinuria, has the disadvantage of causing a decline in GFR and a rise in serum potassium values. Pathophysiological consequences of NS such as hypovolemia, acute renal failure, edema, hypercoagulation, and infections should be treated symptomatically.

4. PATHOGENESIS OF CHILDHOOD NEPHRITIC SYNDROME

In course of NS the glomeruli is unable to filter back albumin or other immune globulins back into blood, rather these molecules pass through the membrane and are found in urine. Albumin is the major blood protein that regulates plasma on tonic pressure; this causes increase in hepatic lipoprotein and transcapillary water level that later on leads to hyperlipidemia and edema conditions linked with NS. Literature explains the role of T-cells in up-regulation of circulating factors (i.e. soluble form of the urokinase-type plasminogen activator receptor (uPAR) and corticotrophin like cytokines of immune cells beside the injury to podocytes due to oxidative stress) or down-regulation of inhibitory factors in reaction to unrevealed immunogens and cytokines. Few potential mechanisms for changes of NS have been suggested by numerous studies in animal models of NS that have indirectly linked to oxidant injury of podocytes. The actual mechanism by which this glomerular membrane gets damaged in primary and secondary form of NS is undefined, but proof robustly relates the importance of genetic factors (i.e. 10%) (Fig. 1.17). A rising number of mutated genes have been recognized that can lead to inherited forms of idiopathic NS. These genes help in guiding different structural proteins or enzymes that work in harmony to manage the glomerular membrane permeability and take part in various signaling events by regulating podocyte enlargement, segregation, communications among cell-cell and cells-matrix interactions. Proteinuria results from the damage caused by these transformations in glomerular filtration barrier and in this event, podocytes require their specific epithelial cell markers such as fibroblast specific protein, nephrin, desmin, actin, collagen, and fibronectin. The findings of these new podocyte proteins and their mutation study have shed light on the pathogenesis of proteinuria linked with NS.

5. SUSCEPTIBLE GENE IN NEPHROTIC SYNDROME

- TRPC6 gene
  - Chromosome location-11
  - Size-42 kb

The TRPC6 (transient receptor potential channel-6) gene is made up of 13 axons that are located on chromosome 11, having 931 amino acids encoding for the short transient receptor potential channel protein with a size of 106325Da. TRPC6 protein is a part of transient receptor potential (TRP) family of action-selective ion channels. TRP subfamily (TRPC1-TRPC7) is expressed in many tissues that
regulate intracellular Ca2+ concentration via G protein-coupled receptors and receptor tyrosine kinesis of this ion channel in podocyte cells and have been recognized as a constituent of the SD. On the basis of their primary conformation, TRP proteins are differentiated into six subclasses; TRPC, TRPV, TRPM, TRPP, TRPML, and TRPA. Further analysis showed that TRPC is subdivided into different consecutive proteins, TRPC1, TRPC4, and TRPC5 or TRPC3, TRPC6, and TRPC7, respectively, that could particularly work together in network form homotetramers and heterotetramers which can interact with several other proteins Activation or modulation of TRPC proteins have been reported to be stimulated by receptor mediated phospholipase C. TRPC are involved in varied biological mechanisms such as cellular growth, maintaining ion homeostasis, PLC-dependent Ca2+ entry into cells, etc. Ca2+ is a secondary messenger that influences many of these cellular functions.

Mutations in TRPC6 gene have been currently found to be associated with to NS. Mutations in this gene were found with autosomal dominant NS. Findings demonstrated 12 different mutations with childhood NS and 4 with late onset of sporadic cases (age of 15-55 years, with a few exception at 1-9 years of age) resulting towards unpredictable rate of development to ESRD In the New Zealand population, nsSNP in axon 2 of TRPC6 gene, causing a proline to glutamine substitution, P112Q was found to be responsible for the disease in all the affected individuals. Through in vitro studies it was proved that, p.P112Q was also associated with exaggerated calcium signaling. If similar results of increase in calcium signaling are observed in vivo, this mutation could lead to a gain-of-function and elevated levels of cellular calcium influx, which may further interrupt glomerular cell functions. TRPC6 gene mutations usually cause a late onset of disease; it may be possible that these variations produce minor intracellular changes that guide to irreversible cell injury. SNP’s, p.N157T and p.A404V showed damaging effect to protein stability by altering gyration and legend binding sites using in silicon based approach.

Almost all the reported mutations were misses, except two p.K874X and 89fsX8 mutations. Eight of these misses mutations (i.e. p.H218L, p.P112Q, p.N125S, p.E897K, p.M132T, p.R895L, p.Q889K and p.R895C) were gain-of-function that cause increase in Ca2+ current amplitudes where as the rest may probably showing pathogenic effect on the basis of biochemical and biophysical variations. Majority of TRPC6 mutations were dispersed all throughout N and C terminal cytosolic domains while no mutation has been observed in transmembrane domains. In European and African families, 6 families were recognized having autosomal dominant FSGS with a distinct misses Varian Thus a controlled cellular regulation of Ca2+ homeostasis by TRPC6 is expected for to normal podocyte function. SNPs in this gene might work as modifiers of proteinuria. Number researchers persuasively showed that TRPC6 activity at the SD is important for proper maintenance of podocyte structure and functions. In context to the earlier identified NS genes which play a role in podocyte cytoskeleton structure or function, TRPC6 is the first calcium-permeable channel gene that has been concerned in NS pathogenesis 1.15.2 NPHS2 gene.

- Chromosome location-1
- Size-25kb

The NPHS2 gene is located on chromosome region 1q25-q31, made of 383 amino acid residues that encodes for podocin. Podocin is a hairpin like integral membrane protein with approx 42 KD, made up of one transmembrane domain and a C-terminal cytoplasmic tail. The 3-prime untranslated portion possessespolyadenylation signals that are placed upstream of the poly(A) tail Comparison of datasets till now demonstrated that the podocin contains an extensively analogous portion between its central region and proteins of the band-7-stomatin family, unlike any other known protein. Within glomeruli the RNA expression of podocin is arrested to the podocytes, but in the developing kidney its expression occurs in time-dependent manner without any signal detected in the earlier stages. This expression enhances future in podocytes with the lower segment of the S-body Producing is an
essential raft-associated component of the podocyte foot-processes, located in the insertion of the SD. It precisely organizes and regulates glomerular membrane structure and interacts with NPHS1, CD2AP, TRPC6 and various other genes. Producing facilitates membrane transport of heparin and directs podocytes intracellular signaling pathways.

Mutations in NPHS2 gene were formerly identified in the children with early NS. Identified NPHS2 gene as causative agent for early onset autosomal recessive steroid resistance form of NS. Overall 6.4-30% of cases were found to have mutations in NPHS2 gene in different parts of the world. From the time when the NPHS2 gene got identified, various researchers in Europe, North America and Middle East confirmed NPHS2 gene mutation taking place in 10-30% of children with sporadic NS). In Initial reports suggested recessive form of NPHS2 mutation in children between 3 months to 5 years of age, but the current data presented its association with a wide range of clinical spectrum in a much larger cohort of patients leading towards ESRD from all over the world. One of the study presented, 9 out of 30 families having NPHS2 gene mutations showing autosomal recessive inheritance pattern with delayed onset of NS. Producing polymorphism p.R229Q is one of most frequently reported one with marginally higher frequency of around 5% in SRNS as compared to healthy individuals. So far more than 50 producing mutations have been account in NPHS2 gene and these reported mutations determine every kind of alteration including misses, nonsense, and deletion. Thus producing protein is spinning out to be a foremost contributor to the genetic trouble of NS.

6. CONCLUSION

Our insight about the etiology of NS is as yet constrained, because of the multifaceted nature and heterogeneity of the hereditary transformations and different elements or systems included. This proposal adds to the unwinding of the etiology of NS inside the setting of South Indian youngsters. The outcomes unequivocally show that the changes and SNP of NPHS1, NPHS2 and MDR1 qualities adds to the pathogenesis of NS. These varieties are promising and would perhaps be considered as likely hereditary hazard components or biomarkers with suggestions in the advancement and movement of ailment. These molecular deformities would give a beginning stage to future examinations to explain the etiology of clinical heterogeneity as well as improve the early discovery of the sickness, recognize the patients with steroid-lethargic NS and avert intense and long haul complexities.

Hereditary communications have been examined a very long time in model living beings as a methods for recognizing their useful connections among qualities or their comparing quality items and furthermore, with the idea of these connections relying upon the kinds of associations. Now and again changes in two qualities produce a phenotype that is amazing in light of every transformation's individual impacts. This marvel, which characterizes hereditary connection, can uncover useful connections among qualities and pathways. Quality communication between different qualities affects the declaration of a living being's phenotype. The hereditary transaction between podocyte qualities and their effect on the clinical phenotype of NS has been recently read with respect to case, both nephrin and podocin may cooperate legitimately or by implication and are significant for upkeep of the glomerular capillary porous hindrance. As far as I could possibly know, there has been no report so far on cooperations between podocyte qualities (NPHS1, NPHS2) in mix with the qualities engaged with directing liquid dissemination (ACE) and medication traffic (MDR1) at the objective cell. Thus, I have broadened the investigation on the communications of podocyte encoding qualities in blend with ACE and MDR1 SNPs, towards steroid responsiveness in NS patients.

Transformations in NPHS1 and NPHS2 qualities, which are the applicant qualities engaged with managing the podocyte structure and capacities in the investigation populace and the outcomes were displayed in part 3 and 4 of this proposal separately. It is imperative to make reference to that 9% and 18% of the SRNS gathering (n=100) demonstrated a change in those particular qualities.
the SNP G2677T/A genotypes of MDR1 demonstrates a relationship to steroid reaction in SRNS patients just among the examination subjects; for example sound volunteers and SSNS gathering. Since the SNP is a triallele, the potential genotypes are homozygous GG, TT, AA or heterozygous GT, GA and TA; of the normal six distinct genotypes, the extent of accessible/larger part in the SRNS subjects are (9% had GG, 34% were TT, 0% were AA, 41% had GT, 11% were GA and 5% were TA genotypes).

Blend of those various genotypes with NPHS1 and NPHS2 change towards the steroid opposition is introduced Figure-6.0. 9% of SRNS patients conveying transformations in NPHS1; among, 7% of them demonstrated the GT genotype and 2% demonstrated the GA genotype for the SNP. Additionally, SRNS patients with NPHS2 changes (18%), 12% of them had the GT genotype, 3% had GA genotype and the rest of the 3% patients had the TT genotype for the SNP. This proposes this SNP both autonomously and in blend with transformations in the NPHS1/NPHS2 qualities is a potential hereditary marker to identify sedate obstruction and responsiveness to steroids.

In the event that our theory is right, at that point one can anticipate a transformation in the applicant qualities (NPHS1 NPHS2) in all the SRNS patients. In any case, just 27% of the patients indicated change in spite of the whole competitor gens (29 exons in NPHS1 and 8 exons in NPHS2) was sequenced. Of which, 17% are novel and has not been accounted for in any populace. It bolsters the idea that the sort and recurrence of change may relies on the way of life or potentially ethnic variety; notwithstanding those competitor qualities different qualities, for example, PLCE1, CD2AP, LAMB2, TRPC6 and numerous different qualities may assume a similarly significant job in controlling the renal physiology and deregulations could brings about NS.

Screening for the regular hereditary reasons for NS will forestall superfluous steroid treatment of these kids. For better comprehension of the relationship between's these quality polymorphisms, allele recurrence and sicknesses conditions, huge associate investigations in various territories should be led. A keen of the molecular systems of the illness may likewise yield new data about etiology and will be useful in creating focused on treatments against the infection.

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