NEPHROTIC SYNDROME

(30 Abstracts)

WCN25-63

REFRACTORY NEPHROTIC SYNDROME IN FOCAL AND SEGMENTAL GLOMERULOSCLEROSIS BY PMM2 GENETIC VARIANT

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Introduction: Nephrotic syndrome (NS) is a clinical condition characterized by massive proteinuria, edema, hypoalbuminemia, and hyperlipidemia. The etiology may be secondary to systemic, metabolic, infectious, neoplastic, and pharmacological diseases. There is a group of primary causes of unknown etiology whose pathophysiological mechanism is immunological whose most frequent histological pattern in adults is focal segmental glomerulosclerosis (FSGS), minimal change disease and membranous nephropathy that represent podocithopathies. Currently, the KDIGO guidelines add that FSGS may have a genetic etiology, which merits a different diagnostic and therapeutic approach due to its refractoriness to immunosuppressive management, determining the causative gene is of great importance to predict its relapse in transplantation. A diversity of genes contributing to podocitopathies (NEPH1, TRPC6, CRB2, FAT1) located in the diaphragm slit has been highlighted, but very few cases have been reported with the PMM2 genetic variant.

Methods:

Clinical case: This is a patient who is currently 37 years old, whose disease began early at 3 years of age, manifested as a nephrotic syndrome, it was managed as if it were a disease of minimal changes, for which she was managed with steroids, with preserved renal function, but with occasional relapses. There is no family history. Later, when she reached the age of majority, she was referred to adult nephrology care. However, with the passage of time he had frequent relapse episodes, for this reason an infectious and autoimmune profile was requested in 2015 that were negative, in addition to a renal biopsy showing a FSGS with podocyte effacement of <50%, and diffuse thinning of the glomerular basement membrane (GBM) (seetable 1), the treatment was optimized by adding calcineurin inhibitor, statin and ARB II, in addition to steroid. However, the patient had fluctuations between partial remissions and relapses, so a rebiopsy was requested in 2018 (Table 1), which highlights the progression of the superior podocyte effacement of 60%, with no alterations in the GBM. An ISGLT2 was added to its baseline management, and its clinical response was torpid again, presenting partial remissions and relapses of the NS. Thus, in 2024, the need to perform genetic and autoimmune studies and perform a rebiopsy is raised, see tables 1 and 2 and image 1. In this biopsy, a podocyte effacement of 80-90% and a segmental thinning of the GBM are highlighted, as for the result of the genetic panel, it was negative for the main highlighted variants, but a finding of a variant in the PMM2 gene was reported, which has been reported in very few cases as a cause of NS.

Results:

Table 1. Summary of Main Biopsy Results

Method	2015	2018	2024
Light Microscopy	- FSGS pattern - Podocyte hypertrophy +++ - Tubule interstitial fibrosis 5% - No vascular alteration - Tubular atrophy 10% - IF with albumin++, IgG++	- FSGS pattern - No glomerular disturbance - Tubular interstitial fibrosis 10% - Tubular atrophy 10% - No vascular alteration - IF with IgG++, IgA+++, C3+	- FSGS pattern - Tubular atrophy - Interstitial fibrosis 10% - No vascular changes
Electron microscopy	- Diffuse slimming MB 185nm - Podocyte effacement <50% - No IC deposits	- MB with normal thickness, occasional double contour - Podocyte effacement >60% - No IC deposits	- MB segmental thinning - Podocyte effacement >80-90% - No IC deposits

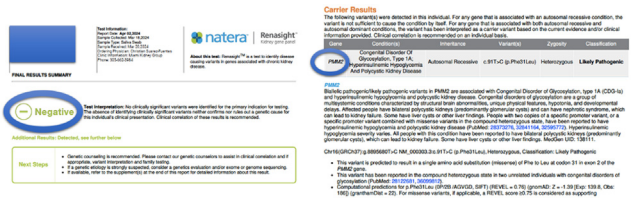
IF: Immunofluorescence, MB: Basement membrane, IC: Immune complexes

Table 2. Autoimmune profile

Parameter	Result
ANCAS	Negative
Anti MPO and PR3	Negative
Anti PLA2R	Negative
C3 and C4	Normal

ANCAS: Anti-neutrophil cytoplasmic antibodies, MPO: Myeloperoxidase, PR3: Proteinase 3, C3 and C4: Complement.

Discussion: The approach to (NS) involves a comprehensive evaluation to identify the underlying etiology, ranging from ruling out infectious, autoimmune and systemic pathologies, to considering primary etiologies and genetic factors(1). Focal segmental glomerulosclerosis (FSGS), a histological pattern of injury, can be classified according to its primary etiology, which is suspected when there is refractoriness to treatment and elevated podocyte effacement(2). Secondary FSGS is caused by infections, medications, or adaptive changes with glomerular hyperfiltration(2). FSGS of indeterminate cause is characterized by podocyte segmental effacement, after ruling out secondary causes(2). Genetic FSGS includes familial, syndromic and sporadic forms, with variants in various genes: NEPH1, TRPC6, CRB2, FAT1, NPHS1, NPHS2, CD2AP, which are located in the "diaphragm slit"(3)(4). The classification of FSGS based on etiology is crucial for guiding treatment and predicting prognosis. In secondary FSGS, identifying and managing the underlying cause is essential(2). FSGS of indeterminate cause may respond to immunosuppressive therapy, although the response is often less favorable compared to minimal change disease(2). Genetic FSGS, particularly when presenting in childhood, is less responsive to immunosuppression and has a higher risk of progression to end-stage kidney disease(3). Genetic testing can help identify the specific mutation and guide counseling regarding recurrence risk and potential for kidney transplantation(4). In conclusion, a thorough evaluation for the etiology of FSGS is essential for appropriate management and prognostication, and further research is needed to elucidate the complex interplay between genetic and environmental factors in the pathogenesis of this disease.



A wide variety of genetic mutations have been reported to cause steroid-resistant nephrotic syndrome (SRNS), allowing us to better understand its pathophysiological mechanisms(5). The suspicion of a genetic etiology should be raised when there is resistance to steroids, a positive family history, extensive podocyte effacement on kidney biopsy, and the presence of extrarenal manifestations(5).Very few cases of SRNS have been reported as a result of variants in the PMM2 (phosphomanomutase 2) gene, which is associated with congenital disorders of glycosylation(6). This is a rare metabolic, systemic entity that can lead to steroid resistance in nephrotic syndrome(6).The identification of PMM2 mutations in patients with SRNS is clinically relevant, as it suggests a specific underlying pathogenic mechanism involving abnormal glycosylation. This knowledge can guide further diagnostic testing and management strategies. Patients with PMM2-related SRNS may benefit from a multidisciplinary approach involving nephrologists, metabolic specialists, and geneticists. Early recognition of the genetic etiology can help avoid unnecessary immunosuppressive treatment and inform prognosis and family counseling. In conclusion, while rare, PMM2 gene variants should be considered in the differential diagnosis of SRNS, especially in the setting of multisystem involvement.

Continued research is needed to fully elucidate the spectrum of genetic causes of nephrotic syndrome and their associated clinical phenotypes.
Conclusions: The importance of performing a genetic panel in patients with (NS) is multifaceted. It provides insights into the underlying pathogenic mechanisms of the disease, which can vary depending on the affected gene. Certain genetic forms of NS are associated with extrarenal features, such as in syndromic forms. Genetic testing can help identify these cases and guide appropriate screening and management of associated conditions. Additionally, it allows for screening of other family members, both to identify asymptomatic carriers and to provide accurate genetic counseling regarding recurrence risks in future pregnancies. Knowing the genetic cause can help avoid unnecessary immunosuppressive therapy in cases of monogenic NS, as these forms are typically resistant to such treatments. In patients with genetic NS, genetic testing is crucial prior to kidney transplantation to assess the risk of disease recurrence in the allograft. This information can guide the choice of donor (living related vs. unrelated) and post-transplant management. In conclusion, genetic testing in NS provides valuable insights that can significantly impact patient management, from diagnosis to treatment and family planning. While not all cases of NS are monogenic, a targeted genetic panel can be a useful tool in selected patients, especially those with early-onset disease, a positive family history, or atypical features.

I have no potential conflict of interest to disclose.

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CLINICAL CHARACTERISTICS IN CHILDREN WITH MONOGENIC AND NON-GENETIC STEROID-RESISTANT NEPHROTIC SYNDROME DUE TO FOCAL SEGMENTAL GLOMERULOSCLEROSIS TREATED WITH CALCINEURIN INHIBITORS

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Introduction: Calcineurin inhibitors (CNI) are currently being considered as the first line immunosuppressive treatment for steroid-resistant nephrotic syndrome (SRNS) in children without a proven genetic cause. According to the latest data, CNI could induce remission and improve outcome in some cases with monogenic SRNS. It remains unclear whether children with monogenic SRNS had higher risk of CNI-induced nephrotoxicity (CNIT). The aim of the study was to compare clinical characteristics in children with monogenic and non-genetic SRNS due to focal segmental glomerulosclerosis (FSGS) treated with CNI.
Methods: A retrospective single-center study was conducted comparing clinical features in 28 children (17F/11M) with monogenic (n=11) and non-genetic (n=17) SRNS with Cyclosporine A (CsA)-induced remission after 12 months of treatment. Kidney biopsy revealed FSGS in all children before genetic testing and start CNI therapy. CNIT was defined by increasing of serum creatinine more than 30% from baseline level. The median of age at onset of SRNS (6.9 vs 5.8 years), disease duration before starting CNI (8.0 vs 7.0 months), baseline serum eGFR (119.0 vs 96.1 ml/min/1.73 m2), CNI dosage (4.2 vs 5.0 mg/kg/d), trough blood CsA levels (138.0 vs 116.1 ng/ml) at the start of CNI treatment and duration of CNI therapy (23 vs 24 months) were similar in two groups of patients (p>0.05). Patients with monogenic SRNS had variants in following genes: *LMX1B* (n=3), *NPHS2* (n=2) and one patient each with variants in *COL4A3, C3, ANLN, CRB2, LAMB2, SGPL1* genes.
Results: The frequency of CNIT (90.9% vs 76.5%, p=0.62), including the incidence of CNIT before the first 6 months of treatment (60% vs 61.5%, p>0.999) in children with monogenic and idiopathic SRNS was comparable. There were no significant difference in the CNI dosage (5.2 vs 5.3 mg/kg/d, p>0.999) and trough blood CsA levels (120.0 vs 128.5 ng/ml, p>0.999), proportion of serum creatinine increasing and eGFR declining from baseline levels (36.5% vs 40.5%; p = 0.337; 24% vs 26%; p = 0.616, respectively) and in the proportion of children with increasing of serum creatinine more than 50% from baseline level (60% vs 69.2% p = 0.685) at the time of acute CNIT in two groups. We did not find any significant differences between children with monogenic and non-genetic SRNS in the proportion of serum creatinine increasing and eGFR declining from baseline levels (26.5% vs 14.2%; p = 0.445; 5.7% vs 3.2%; p = 0.835, respectively) and in the proportion of children with increasing of serum creatinine more than 25% from baseline level (60% vs 30.8% p = 0.222) after CNI dosage adjustment followed by withdrawal of CNI. The frequency of irreversible CNIT with continued decline of eGFR after CNI withdrawal in children with monogenic and idiopathic SRNS was also comparable (36.5% vs 35.3%, p>0.999).
Conclusions: In spite of using therapeutic dosage and drug monitoring of CsA in all children with monogenic and non-genetic SRNS due to FSGS, the frequency of CNIT was higher than 70% in two groups of patients. The incidence and course of CNIT in patients with monogenic and non-genetic SRNS was similar, which allow us to use CNI to induce remission of the disease in these children. Performing measurement of trough blood CsA levels and serum creatinine is required to make timely dosage adjustment or withdrawal of CNI.

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CLINICAL AND HISTOPATHOLOGICAL CHARACTERISTICS AND OUTCOMES OF PRIMARY IMMUNE-COMPLEX-MEDIATED MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS IN CHILDREN

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Introduction: Immune-complex-mediated membranoproliferative glomerulonephritis (IC-MPGN) is an ultra-rare, fast-progressing kidney disease resulting from immunoglobulin/immune complex deposition triggering complement activation. Data regarding clinical course and long-term outcome in children with IC-MPGN is still scarce. The aim of the study was to investigate clinical and histopathological characteristics and kidney outcomes in children with primary IC-MPGN.
Methods: We conducted retrospective study of 19 (8M/11F) children with IC-MPGN diagnosed between 2012 and 2019 years. The median age at onset of the disease was 11.0 (IQR: 8.0; 14.0) years. The median duration of the disease before kidney biopsy was 6.0 (IQR: 3.5; 14.0) months. Kidney biopsy with light microscopy and immunofluorescence was performed in all patients. Electron microscopy was done in 11/19 (57.9%) children. All patients were treated with intravenous (iv) cyclophosphamide (CYC) at a dose of 500 mg/m2 for monthly infusion for 6 months combined with oral steroids (1 mg/kg/48h). The median follow-up was 24.0 (IQR: 15.6; 46.8) months.
Results: All patients presented with steroid-resistant nephrotic syndrome (SRNS) with hematuria and hypertension. 7 (36.8%) children had elevated serum creatinine level at onset of IC-MPGN. Light microscopy revealed along with glomerular basement membrane double contours accompanied by endocapillary and mesangial hypercellularity in all cases, focal glomerulosclerosis in 14 (73.7%) patients, tubular dystrophy and atrophy in 14 (73.7%) and 5 (26.3%) patients, respectively, and interstitial fibrosis in all subjects, including focal - in 15 (78.9%) and diffuse - in 4 (21.1%) individuals. Immunofluorescence showed capillary loop and mesangial deposition of IgG with or without IgM and, to a lesser extent, C3 in all individuals. Electron microscopy demonstrated thickening of glomerular capillary walls due to subendothelial deposition of immune complexes with diffuse (6/11 (54.6%)) or focal (5/11 (45.4%)) podocyte effacement. The first line of immunosuppressive treatment with iv CYC induced complete (CR) and partial remission (PR) of IC-MPGN in 5 (26.3%) and 4 (21.1%) patients, respectively. There was no effect of CYC treatment in 10 (52.6%) children. At the end of follow-up CKD-1 was found in 7 (36.8%) patients with IC-MPGN; CKD-2 in 7 (36.8%) children; CKD-3 in 4 (21.1%) subjects, and CKD-5 in 1 (5.3%) case. Increase in eGFR slope during follow up had 8 (42.1%) children (median 6.0 (IQR: 11.4; 1.8) ml/min/1.73 m2 per year). Decrease in eGFR slope during follow up found in 11