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Mini-Review

Non-Palliative Treatment and Follow-Up of Children with Genetic Forms of Nephrotic Syndrome: A Narrative Mini-Review

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Abstract

Nephrotic syndrome is the major clinic presentation of glomerulopathies in childhood. Steroid-unresponsiveness is the main indication for kidney biopsy and is closely related to genetic causes. However, the identification of more than 60 genes in the last 2 decades led to the need of new approaches to delay progression to chronic kidney disease and the need for kidney replacement therapy. The current review aimed to identify non-palliative therapeutical approaches to genetic forms of nephrotic syndrome in children and their follow-up. Genetic mutations play a significant role in the pathogenesis of nephrotic syndrome, influencing the choice of treatment strategies and individual patient outcomes. Calcineurin-inhibitors, coenzyme Q-10 supplementation and other drugs may reduce proteinuria and decrease the progressive decline of glomerular filtration rate.

***Keywords:** Steroid, Resistant nephrotic syndrome, Children, Genetic heterogeneity, Treatment*

Introduction

Massive proteinuria and oedema are the hallmark of nephrotic syndrome (NS) in childhood and remains a major clinical challenge in steroid resistant patients. Monogenic causes of NS are rare, 10-15% of all children with NS [1] but specifically in cases of steroid resistant nephrotic syndrome (SRNS), where up to 30% of monogenic etiologies were already described [2]. Currently more than 60 genes are recognized as genetic causes of NS [3]. However, the clinical presentation, age of onset as well as commitment of other organs vary among them. These findings led to the KDIGO recommendation of genetic testing in some situations as follows: NS in children bellow 1 year of age; primary steroid resistance; familial history of NS and syndromic features [4]. These indications exclude commonly observed situations, e.g., late steroid resistance. The term “genetic analysis” is broad and include:

- Next generation panel sequencing (NGS), allowing the analysis of a limited number of genes, previously identified as related to NS. The main advantage of this choice relies on its cost in comparison to other methods.

- Whole exome sequencing (WES), which may identify not only pathogenic variants in coding regions, but also the eventual presence of phenocopies, a situation where there is a discrepancy between the patient’s genotype and phenotypic manifestations. This phenomenon is relatively rare but important for the follow-up, since other organs may also be affected, e.g., in COL4A variants [5]. Phenocopies represent a disruption in the phenotypic manifestation of the genotype. Pathogenic variants related to clinical manifestation as SRNS include COL4A5, COL4A3, CLCN5, GLA, AGXT, CTNS, FN1 and WDR19 [5].

- Whole genome sequencing (WGS), which also permits recognition of pathogenic modifications in non-coding regions of the gene.

The American College of Medical Genetics and Genomics suggests the use of “pathogenic variant” instead of “mutation” in genetic analysis and throughout this review its use will be related to monogenic causes of SRNS previously described in literature [6].

The current narrative review aims to identify the most common genetic forms of NS in childhood described in literature and the non-palliative therapeutic approaches to these patients.

Methods

The present article is a narrative review with articles retrieved from the last 10 years (2013-2023) in the PubMed as well as EBSCO Databases and complementary references. The following MESH terms were chosen for the search: (("therapeutics" OR "treatments" OR "therapy") AND ("genetic" OR "genetical" OR "genetically" OR "genetics") AND ("forms") AND ("nephrotic syndrome" OR ("nephrotic" AND "syndrome") OR "nephrotic syndrome" AND ("child" OR "children" (2013:2023[pdat]) AND genetic: "genetic OR "genetical" OR "genetically" OR "genetics" .

Palliative treatment of genetic forms of NS was considered as those mainly directed to oedema and proteinuria control without direct action on the podocyte, but through changes in intraglomerular dynamics e.g., non-steroidal anti-inflammatory drugs (NSAIDs), renin-angiotensin-aldosterone inhibitors (RAAS-i) and/or or angiotensin II - receptor blockers (ARBs) as well as unilateral nephrectomy.

Results and Discussion

Most frequent genes

Initially 45 articles were retrieved from the period 2013-2023 and posteriorly grouped and summarized with the Rayyan Platform [7], from which 38 were excluded due to following criteria: articles devoted to adult population; lack of detailing of therapeutic approaches; exclusive use of palliative treatment as defined above; treatment involving animal or experimental models.

Currently, the largest international registry devoted to genetical analysis of SRNS in childhood is the PodoNet Registry [1]. The most common monogenic causes of SRNS in the registry were pathogenic variants in NPHS2, WT1 and NPHS1, which are responsible for 42, 16, and 13% of cases, respectively of all cases. Similar results were also observed in other studies [8,9]. Identification of genetic variants permits a proper precision medicine and treatment individualization [10].

Therapeutical Options

Calcineurin inhibitors

This category includes 3 drugs, cyclosporin A, tacrolimus and voclosporin, which has not been tested in patients with genetic forms of NS.

Cyclosporin A exerts its effect through binding to cyclophilin A , while tacrolimus bonds to an immunophilin, FK506 binding protein (FKBP) [11,12]. These two distinct modes of action may explain why cyclosporin does not induce complete remission in some patients but tacrolimus does. However, this difference was not observed in a meta-analysis by Liu et al [13].

The induction of remission, partial or complete, is in fact much more common than expected in certain sub-sets of patients with SRNS, as reported by Malakasioti et al in a systematic review [14]. Patients with WT1 variants have a 5-fold chance of remission when compared to patients with other variants. In this study, a partial or complete remission varied among patients with distinct variants: NPHS1 (30-40%), NPHS2 (20-30%), PLCE1 (50%), WT1 (70%) and TRP6 (20%). This observation sustains the recommendation of first line drugs after the diagnosis of steroid resistance, even when genetic analysis is not available.

The response to this group of drugs is also influenced by other factors, e.g., interaction between polymorphic NPHS2 gene and COL4A3 [15,16]. However, the type of variant (exonic and intronic or nonsense, missense, and splicing variants) did not influence the response rate as described by Malakasioti et al [14]. The association of cyclosporin and other drugs with a distinct mechanism, e.g., Rituximab, is still not considered as superior to the traditional option for cyclosporin alone [17,18].

Mycophenolate mofetil

Mycophenolate mofetil / sodium mycophenolate are antiproliferative agents used mainly in solid organ transplantation and in lupus nephritis. The active metabolite is the mycophenolic acid, which inhibits B and T-cell proliferation and it may also suppress antibody production [9]. It also interferes with cytokines production. A meta-analysis conducted by Liu et al did not show any advantage over CNI except by the reduction of side effects [13].

Agents targeting pathways by specific pathogenic variants

Coenzyme Q10 supplementation

The actin cytoskeleton in podocytes depends on a set of actin binding proteins, nucleators and inhibitors of actin polymerization as well as regulatory GTPases. The main metabolic system in mitochondria involves lipophilic molecules named Coenzymes Q and are also located in the Golgi apparatus and cell membranes [19]. Variants in distinct genes responsible for these molecules, e.g., COQ2, COQ4, COQ6, COQ7, COQ9, PDSS1, PDSS2, aarF domain containing kinase 3 [ADCK3], and ADCK4, are associated with proteinuria [12-14]. Pathogenic variants of CoQ6 are associated with sensorineural deafness and SRNS [20-22]. Supplementation with CoQ10 may attenuate proteinuria and preserve renal function. Reduction of proteinuria was achieved in ADCK4-knockout mouse model with 2,4-Dihydroxybenzoic acid treatment [23].

Conclusion

The development of technology allowed the recognition of an important group of monogenic causes of steroid-resistant nephrotic syndrome in children. Contradicting old concepts, the therapeutical arsenal to treat these genetic conditions increased in the last decade and allowed individual approaches to each group. Calcineurin-inhibitors are the most used drugs, with partial or even complete remission of proteinuria. Supplementation of CoQ10 also induces improvement of the clinical condition in pathogenic variants involving the CoQ system. Genetic analysis, either exome-sequencing or NGS, when available and accessible to the family, is mandatory.

Conflict of Interest

The authors declare no conflict of interest.

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