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ANALYSIS OF CLINICO-PATHOLOGICAL CORRELATIONS OF CONGENITAL AND INFANTILE NEPHROTIC SYNDROME IN PAKISTAN

[1]Dr. Memoona Akhtar, [2]Dr. Hira Buzdar, [3]Dr. Ammara Shaukat

[1]Women Medical Officer at RHC Lessar Kalan, Narowal

[2]Women Medical Officer at THQ Hospital, Kotaddu, Muzafargarh

[3]Women Medical Officer at THQ Hospital, Sangla Hill

Abstract:

Introduction: *Nephrotic syndrome is characterized by gross proteinuria, hypo albuminemia, hyperlipidemia, and peripheral edema. The etiology of nephrotic syndrome in adults is complex and ranges from primary glomerulonephritis to secondary forms.*

Objectives of the study: *The basic aim of the study is to analyze the clinico-pathological correlations of congenital and infantile nephrotic syndrome in Pakistan.*

Material and Methods: *This study was conducted at hospitals of Narowal, Pakistan during 2018. This was done with the permission of ethical committee of hospital. The data was collected from 100 children who presented within the first year of life with nephrotic syndrome who had a histological diagnosis obtained by renal biopsy in the hospital. The clinical diagnosis of NS was made on the basis of nephrotic range proteinuria, hypo albuminaemia and oedema.*

Results: *Seventy children who presented at 0.1–11.6 (median 1.6) months were included with 31 presenting within the first three months of life. Histopathological review diagnostic categories were; 13 Mesangial proliferative glomerulopathy (MesGN), 12 Focal and segmental glomerulosclerosis (FSGS), 11 Finnish type changes, eight Diffuse Mesangial Sclerosis (DMS), three Minimal change disease (MCD) and one each of Dense Deposit Disease (DDD) and Membranous nephropathy.*

Conclusion: *Nephrotic syndrome can increase your child's risk of infection and blood clots. Children with identified causative mutations generally presented earlier and had poor renal outcome. The time taken to obtain genetic testing results is decreasing with improving technology. The availability of genetic testing varies from centre to centre and country to country.*

Keywords: *Analysis, Clinico-Pathological, Correlations, Congenital And Infantile, Nephrotic Syndrome, Pakistan.*

Corresponding author:

Dr. Memoona Akhtar,

Women Medical Officer at RHC Lessar Kalan, Narowal

QR code

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INTRODUCTION:

Nephrotic syndrome is characterized by gross proteinuria, hypo albuminemia, hyperlipidemia, and peripheral edema. The etiology of nephrotic syndrome in adults is complex and ranges from primary glomerulonephritis to secondary forms. Primary forms of nephrotic syndrome in adults are comprised of three histological disease entities: idiopathic membranous nephropathy (iMN), minimal change disease (MCD), and focal segmental glomerulo sclerosis (FSGS) [1]. The basis for therapy of primary nephrotic syndrome is mostly of supportive nature. Supportive strategies include antihypertensive and anti-proteinuric therapy and dietary recommendations [2].

Nephrotic syndrome (NS) which appears early in life provides a diagnostic and management challenge to pediatric nephrologists. It is caused by heterogeneous glomerular diseases, and the diagnosis is based on clinical, laboratory, and histological criteria. Congenital nephrotic syndrome (CNS) is a term used for NS presenting within the first three months of age while infantile nephrotic syndrome (INS) is used for NS presenting between three and 12 months of age [3].

CNS and INS are commonly associated with Finnish type nephropathy or Diffuse Mesangial Sclerosis (DMS) on histological examination. However, other glomerular pathologies have also been reported such as focal and segmental glomerulosclerosis (FSGS) and minimal change disease [4].

Patients with nephrotic syndrome are also at increased risk to develop thromboembolism. In patients with membranous nephropathy, the adjusted hazard ratio for thromboembolism was 10.8 compared to patients with IgA nephropathy [5]. In contrast, for patients with FSGS the hazard ratio was 5.9. Hence, anticoagulant therapy is recommended in patients with a primary nephrotic syndrome, especially in iMN and serum albumin < 2.5 mg/dl. The presented model takes into account the serum albumin concentration, the individual patient's bleeding risk, and the risk tolerance as reflected by the selected benefit-to risk ratio [6].

Theoretical Background

Idiopathic, or primary, nephrotic syndrome is often used to describe the group of patients for whom no specific cause has been identified, and the histology is relatively non-specific[4]. These patients will usually receive immunosuppression without knowledge of the mechanism and be categorized according to response. So the challenge is to understand and categorize the underlying injury at a molecular level and therefore adapt treatments according to the likely mechanism[7].

Objectives of the study

The basic aim of the study is to analyze the clinico-pathological correlations of congenital and infantile nephrotic syndrome in Pakistan.

MATERIAL AND METHODS:

This study was conducted at hospitals of Narowal, Pakistan during 2018. This was done with the permission of ethical committee of hospital. The data was collected from 100 children who presented within the first year of life with nephrotic syndrome who had a histological diagnosis obtained by renal biopsy in the hospital. The clinical diagnosis of NS was made on the basis of nephrotic range proteinuria, hypo albuminaemia and oedema. Clinical management over the years before genetic testing was available usually included a renal biopsy in patients with CNS or INS unless clinical management with early nephrectomy was planned. However, this clinical practice was modified with priority given to genetic studies in recent years.

Clinical, laboratory, and histological data were collected from the medical notes of the patients, including age, renal function, and quantification of albuminuria at onset of the disease and at the time of renal biopsy. Data was recorded on family history, antenatal history, birth weight, and treatment, clinical and long-term follow-up. Extra-renal manifestations (neurological, ophthalmological, hepatic, and gastro-intestinal involvement) were evaluated from the notes.

Statistical analysis

Student's t-test was performed to evaluate the differences in roughness between group P and S. Two-way ANOVA was performed to study the contributions. A chi-square test was used to examine the difference in the distribution of the fracture modes (SPSS 19.0 for Windows, SPSS Inc., USA).

RESULTS:

Table 01 explains the basic demographic characteristics of patients. Age range of patients was 1-18 years with a mean of 8.11 $\pm$3.58 years. Patients underwent renal biopsy also. Patients with focal segmental glomerulosclerosis (FSGS) were least likely to respond to treatment followed by mesangio proliferative glomerulonephritis and minimal change disease.

Table 01: Analysis of demographic characters of patients

	Age	Age at first renal histology (months)	Number of glomeruli	UA: UC (mg/mmol) at presentation	Family history	Parental consanguinity	Steroid treatment
MesGN	0.8 (0.1-7.2)	5.5 (1-8)	20 (5-105)	2600 (460-20400)	3(23.1 %)	4(30.8 %)	1 (7.7 %)
FSGS	1.5 (0.1-9.9)	5 (2-16)	31 (13-56)	2910 (644-3444)	(0 %)	4 (40 %)	0 (0 %)
Finnish	1.0 (0.0-4.8)	7 (3-16)	27 (5-100)	5945 (2900-8460)	1(9.1 %)	4 (36.4 %)	1 (9.1 %)
DMS	4.7 (0.2-11)	6.5 (1-13)	21 (5-50)	6473 (2133-7600)	1 (12.5 %)	1 (12.5 %)	2 (25 %)
MCD	9.3 (0.5-10.1)	10 (1-17)	42 (15-65)	3178 (1225-3400)	0 (0 %)	2 (66.6 %)	2 (66.6 %)
Other	3-11.6	3-12	47-106	459-5461	0 (0 %)	0 (0 %)	1

The histological diagnosis and outcome of the five children who had genetic testing performed but without identified causative mutations (table 02). All patients with causative NPHS1 mutations had at least one severe (nonsense or splice site) mutation, except for the patient with the homozygous R367C mutation, which has been previously shown to cause aberrant trafficking of nephrin.

Table 02: Outcome and findings in children without identified causative mutations

Pathology	Mutation found	age at biopsy (months)	Outcome
FINISH	Hetrozygous NPHS1 variant (c.320C>T;p.Ala107Val)	7	Dialysis at 10 months of age
FSGS	None	2	Dilaysis at 3 months of gae and died from sepsis at 9 months of age
MESGN	None	5	Remission
DMS	Heterozygote NPHS1 variant (c.1223G>A;p.Arg408Gln)	10	Dialysis at 15 months of age
MEMBRANOUS	None	12	Remssion

DISCUSSION:

There have been no consistent clinical cues to either whether a patient with nephrotic syndrome has the risk of becoming steroid-resistant in the future or whether they will suffer recurrence post-transplant[8]. CNS and INS are commonly associated with Finnish type nephropathy or Diffuse Mesangial Sclerosis (DMS) on histological examination. However, other glomerular pathologies have also been reported such as focal and segmental glomerulosclerosis (FSGS) and minimal change disease (MCD) [9].

Early onset NS is usually caused by a genetic defect in a major podocyte slit diaphragm protein, Nephrin (NPHS1), or less commonly by mutations in WT1, PLCE1, LAMB2 or NPHS2. Non-genetic causes include infections such as congenital toxoplasmosis, cytomegalovirus infection, or congenital syphilis [10]. In addition, there are children with congenital NS who spontaneously improve: some of these patients may have anti-glomerular antibodies transferred from the mother, although in many children, the reason for developing NS is unexplained [11].

A renal biopsy in children under 12 months of age

with NS can, however, be technically difficult to perform, with potentially serious complications, especially in small oedematous children. The clinical utility of the biopsy result with respect to prognosis and management is unclear in the era of increased genetic testing [12]. Nephrotic syndrome (NS) is not a disease in itself; rather, it is a group of kidney-related findings in your child's body that indicate damaged glomeruli (kidney's filter) resulting in too much release of protein from the blood into the urine [13]. This leads to edema (swelling), high cholesterol levels, high levels of protein in urine (proteinuria) and low levels of protein in blood (hypoalbuminemia). Nephrotic syndrome can be categorized into two subtypes, which further divide into various diseases and circumstances that damage the glomeruli [14].

CONCLUSION:

Nephrotic syndrome can increase your child's risk of infection and blood clots. It always affects both kidneys and usually appears in the early years of your child's life. Most children with this disorder outgrow it by young adulthood. Children with identified causative mutations generally presented earlier and had poor renal outcome. The time taken to obtain genetic testing results is decreasing with improving technology. The availability of genetic testing varies from centre to centre and country to country.

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