WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 7.421
Volume 8, Issue 3, 175-203 Research Article ISSN 2278 – 4357

NEPHROTIC SYNDROME IN SULAIMANI PEDIATRIC TEACHING HOSPITAL

Dr. Ali Qais Abdulkafi*, Dr. Adnan Mohammed Hasan Hamawandi and Dr. Baker R. Rasheed

[1]M.B.Ch.B.
[2]Professor of Pediatrics, M.B.Ch.B. C.A.B.Ped
[3]M.B.Ch.B. F.I.B.M.S. H.D.P.

Article Received on
13 Jan. 2019,
Revised on 04 Feb. 2019,
Accepted on 25 Feb. 2019
DOI: 10.20959/wjpps20193-13296

***Corresponding Author**
Dr. Ali Qais Abdulkafi
M.B.Ch.B.

ABSTRACT

Background: Nephrotic syndrome (NS) is clinical manifestation of different histopathological subtypes. (NS) is characterized by proteinuria and hypoalbuminemia leading to edema. Hyperlipidemia, are usually associated. Most patients with (NS) have frequent relapses until disease resolve spontaneously toward the end of second decade of life and the main problem is their complications or side effects of drugs used, they suffer the influence of proteinuria, caused by the increase of the glomerular permeability. The therapy of (NS) is still a matter of controversy. **Objective:** To analyze the trend of histopathological subtypes in idiopathic nephrotic syndrome & to assess the options of treatment. **Patients and Methods:** This case series study was performed in Sulaymaniyah pediatric teaching hospital carried out over 10 months study period, started from 1st of Jan. to 30th of Oct. 2015 diagnosed with (NS) &/or treated and followed up in the pediatric consultation clinic through clinical examination and investigation. The following data parameters were collected (age, gender, initial episode, duration of disease, relapses, predisposing factors, family history of (NS), clinical presentation, investigation, treatment and complication). Patients with (NS) were involved in the study & the patients with other renal pathology were excluded from the study. We compare between each patient according to individual type of pathology and to the response to medication used. **Results:** The total number of patients involved was 17. Ten males (59%) and 7 females (41%) with male to female ratio 1.4:1. Age range between 2-18 years, with peak incidence at age group from 3-5 years. Age at onset ranged between 10 months-8 (median 4) years. Family history of (NS) was reported in 4 cases (23.6%). The numbers of patients presented with initial attack 1

(5.9%), while the rest with relapse. The main type of presentation was periorbital oedema. Hypertension was presented in 11 patients (64.7%), and only 6 patients (35.5%) had normal blood pressure. Steroid therapy was given to all patients, followed by Every Other Day Steroid (EODS). Steroid sensitive (NS) was found in 9 (52.9%), steroid dependent (NS) and steroid resistant (NS) in 6 (35.3%) and 2 (11.8%) respectively. Regarding the type of pathology, 11 patients (64.7%) were unknown biopsy (not down). Three patients (17.6%) showed minimal change disease, and other 3 (17.6%) focal segmental glomerulosclerosis. According to histopathology, the patients with unknown etiology had higher rate of response, patients with FSGS mostly resistant, and patients with MCNS show dependant on steroid. Respiratory tract infection was reported in 9 cases (52.9%), 6 patients (35.3%) had urinary tract infection, one patient (5.9%) developed septicemia. **Conclusion:** (NS) is a chronic disease with suffering a relapsing course and being at risk of frequent courses of prednisolone therapy with increase risk of side effect & complications. The drugs used are the common drugs and EODS is preferable type of medication used in SRNS. The trend of histopathological patterns has profound prognostic significance and has significant implications in the management of childhood (NS). Our finding is in agreement with the recommendation of performing renal biopsies on children with idiopathic nephrotic syndrome who are steroid dependant in addition to those who are steroid resistant particularly before starting cytotoxic medication.

KEYWORDS: nephrotic syndrome (NS)**,** every other day steroid (EODS), steroid sensitive nephrotic syndrome (SSNS), steroid resistant nephrotic syndrome (SRNS).

INTRODUCTION

(Definitions)

Nephrotic syndrome: is the clinical manifestation of glomerular diseases associated with heavy (nephrotic-range) proteinuria. Nephrotic range proteinuria is defined as proteinuria >3.5 g/24 hr or a urine protein: creatinine ratio >2. The triad of clinical findings associated with nephrotic syndrome arising from the large urinary losses of protein are hypoalbuminemia (≤2.5 g/dL), edema, and hyperlipidemia (cholesterol >200 mg/dL). The association of heavy protein-uria and hypoalbuminemia & the response to therapy were classified according to the definition from the British Pediatric Nephrology Association.

Remission: Proteinuria < 4 mg/h/m² or 0-trace on Albustix for 3 consecutive days.

Steroid sensitive: Complete resolution of protein-uria within 4 weeks of Prednisolone therapy.

Steroid resistant: Failure to respond after 4-8 weeks of Prednisolone 60mg/m/day.

Steroid dependence: Recurrence of nephrosis when the dose of Prednisolone is reduced or within 2 weeks after discontinuation of therapy.

Frequent relapses: 2 or more episodes of nephrosis within 6 months of the initial response or 4 or more within any 12 months period.[3]

Nephrotic syndrome (N.S.) may be caused by primary (idiopathic) renal disease or by a variety of secondary causes. Patients presented with marked edema, protein-uria, hypoalbuminemia, and often hyper-lipid-emia. Treatment of most patients should include fluid and sodium restriction, oral or intravenous diuretics, and angiotensin-converting enzyme inhibitors.[4]

Nephrotic syndrome is clinical manifestation of different histopathological subtypes. Male to female ratio was 1.2/1. and defined by the association of a protein-uria higher than 3.5 g / 24 hours, hypoalbuminemia, oedema and dyslipidaemia. Primary glomerular diseases associated with Idiopathic Unknown Nephrotic syndrome 90**%**.[5][6]

MAIN common cause of primary etiology

A. Minimal change disease glomerulopathy >80% (MCDGP).
B. Focal and segmental glomerulosclerosis 10-20% (FSGS).
C. Diffuse Mesangioprolefrative Glomerulonephritis. 5% (DMPGN).

Table 1. Histologic Patterns and Features of Primary Nephrotic Syndrome

Histologic pattern	*Key pathologic features*	*Key clinical features*
Focal segmental glomerulosclerosis	Sclerosis and hyalinosis of segments of less than 50 percent of all glomeruli on electron microscopy	May be associated with hypertension, renal insufficiency, and hematuria
Membranous nephropathy	Thickening of the glomerular basement membrane on electron microscopy; immunoglobulin G and C3 deposits with immunofluorescent staining	Peak incidence at 30 to 50 years of age; may have microscopic hematuria; approximately 25 percent of patients have underlying systemic disease, such as systemic lupus erythematosus, hepatitis B, or malignancy, or drug-induced nephrotic syndrome
Minimal change disease	Normal-appearing glomeruli on renal biopsy microscopy; effacement of foot processes on electron microscopy	Relatively mild or benign cases of nephrotic syndrome; may occur following upper respiratory infection or immunization

Information from reference [4]

Other RARE primary etiology or Cause[7]

Membranoproliferative Glomerulonephritis

Primary glomerular diseases

Membranous glomeruli-nephro-pathy

Global Mesangeal sclerosis

IgA nephropathy

C1q glomerulopathy

Fibrillar glomerulopathy

Congenital podocyte anomaly

Monoclonal Gammopathy of uncertain significance MGUS, amyloidosis

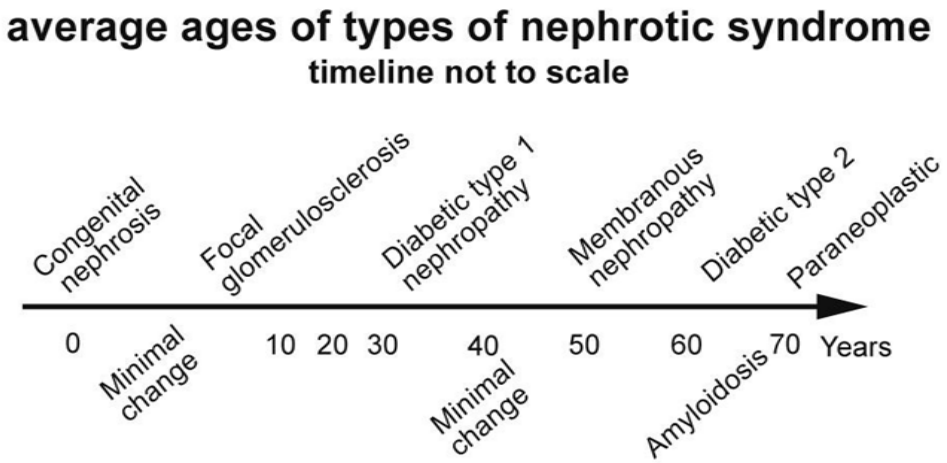

Figure 1 A scheme of the average patient ages associated with various common forms of Nephrotic syndrome.[9]

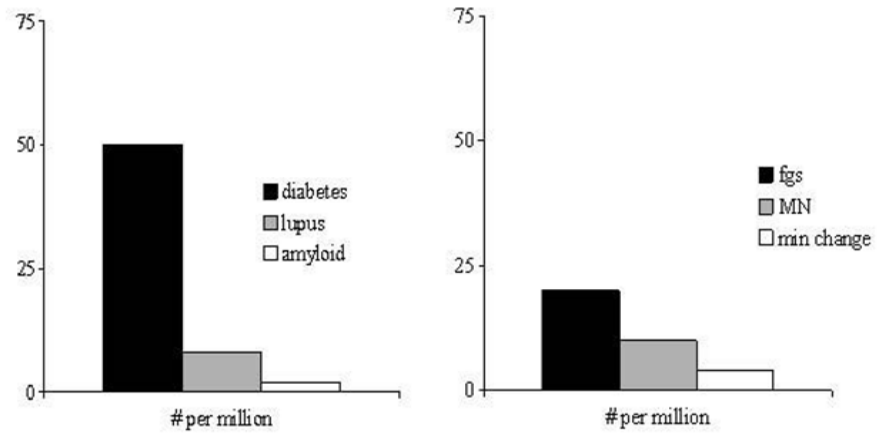

Figure. 2: Incidence of causes of N.S, in number per million populations. Systemic on the left and primary renal diseases on the right. Fgs = focal glomerulosclerosis, MN = membranous nephropathy, min change = minimal-change nephropathy.[9]

Nephrotic syndrome is mainly a disease of childhood and its occurrence in children (15) time more than adult. The increased occurrence of Urinary tract infection (U.T.I.) are due to immunoglobulin loss, defective T cell function, immune suppressive agents, relative malnutrition which occurs due to anorexia and vomiting and other factors.[11]

Patients with positive family history of Nephrotic syndrome forms 6.3% of idiopathic Nephrotic syndrome, with response to steroid therapy, frequency of relapse and histopathological equivalent to MCNS or FSGS similar to sporadic cases of idiopathic Nephrotic Syndrome.[12]

There is a significant association between mothers' practices and their educational level, and duration of the child's disease. While mother's age, occupation, child's age, sex, age at onset (years), and previous heredity disease have no association with their practices.[13]

Pathophysiology is an immune mediated kidney disease associated with T cell dysfunction and secondary disturbance of B cell that leads to changes in levels of immunoglobulins. Increase in albumin-uria accompanied by a reduction in IgG level. While, a direct proportional relationship was found between the degree of albumin-uria and the mean concentration of serum Immunoglobulin M (IgM) when there is an increase in albumin-uria it is associated with elevation of IgM level).[14]

Albumin is a protein that acts like a sponge, drawing extra fluid from the body into the bloodstream where it remains until removed by the kidneys. When albumin leaks into the urine, the blood loses its capacity to absorb extra fluid from the body, causing edema. Nephrotic syndrome can also be caused by systemic diseases, which are diseases that affect many parts of the body, such as diabetes or lupus. More than 50 % of N.S. in adults, with diabetes being the most common.[15]

With the single urine sample, the lab measures both albumin and Creatinin, a waste product of normal muscle breakdown. The comparison of the measurements is called a urine albumin-to-Creatinin ratio.

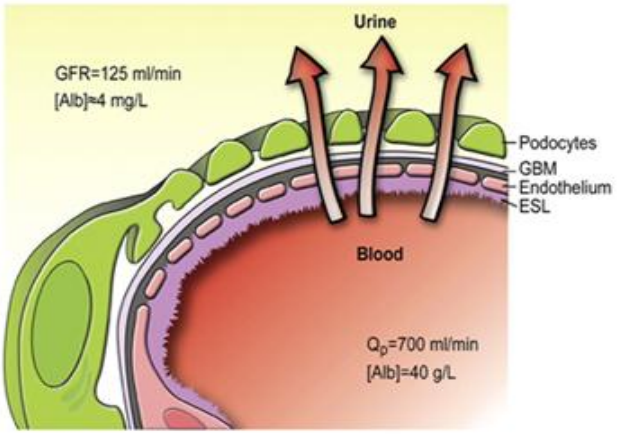

Figure. 3: Schematic drawing of the glomerular barrier. GBM glomerular basement membrane; ESL = endothelial cell surface layer (glycocalyx). QP = Plasma flow rate. Urine is formed through filtration of plasma fluid across glomerular barrier (arrows).[8]

Complications of Nephrotic Syndrome

People with Nephrotic syndrome should receive the pneumococcal vaccine, which helps protect against a bacterium that commonly causes infection, and yearly flu shots. The loss of different proteins from the body can lead to a variety of complications in people with Nephrotic syndrome. Like Hypothyroidism, iron-resistant microcytic hypochromic Anemia, Coronary Artery Disease, hypertension & Acute Kidney Injury. Loss of immunoglobulins—immune system proteins that help fight disease and infection—leads to an increased risk of infections. These infections include pneumonia, Cellulitis, peritonitis, and septicemia & meningitis. Urinary tract infection was the most common complication.[17]

The hypercoagulable state associated with the Nephrotic syndrome is caused by an increased urinary loss of anti-thrombin III, and increased platelet aggregation. The patient with acute renal vein thrombosis can present with sudden onset of flank or abdominal pain, gross Hematuria, and an acute decline in renal function, but most patients are asymptomatic. Pulmonary emboli, Strokes and myocardial infarctions are also can occur.[18]

Development of hypertension among frequent relapse patients and steroid dependent on maintenance steroid therapy was high that effective treatment of these patients is still far from optimal. The clinician who cares for those children must strive to maintain difficult balance between therapeutic effectiveness while avoiding undesirable medical consequences.[19]

Indication of Renal Biopsy[20]

1. Steroid resistance. No response to 6 weeks daily divided dose of steroid therapy.
2. Age less than 1year or older than 8 years.
3. Unusual presentation (such as significant elevation of serum Creatinin, Persistent microscopic or gross Hematuria). Hypertension
4. Steroid dependant nephritic and frequent relapser NS.
5. Glomerulonephritis suspicion
6. Renal manifestations of systemic diseases
7. Acute renal failure!
8. Low Complement 3 Level serum level.
9. Before decide to give cytotoxic drugs.

Contraindications (C.I.)[21]

Relative

Uncontrolled hypertension

Renal abscesses

Pyelonephritis

Hydronephrosis

Marked obesity

Severe anemia

Uremia, polyarteritis nodosa

Large renal tumors or cysts

Solitary Atrophic kidney

Skin infection at biopsy site

Acute and chronic renal failure

Absolute

Bleeding diathesis

Anatomic abnormalities

Uncooperative behavior

Pregnancy

Diabetes

The observed increase in NS in recent years could be explained by environmental factors such as antigen-driven mechanism: infective antigen as well as food or other allergens.[22]

Other systemic diseases, such as Systemic Lupus Erythematosus (SLE), amyloidosis, hepatitis B and C, Human Immune-deficiency Virus, neoplasms or hematologic diseases may also be associated with glomerular disorders causing N.S. Drugs or toxic substances must be considered (bisphosphonates, Non-Steroidal Anti Inflammatory Drug, heavy metals etc).

Theoretically renal biopsy is therefore mandatory for every Nephrotic patient except in contraindicated patient, in order to define the disorder accurately and optimize treatment.

Treatment: There was no isolated 100% effective drug and the drugs used affected by their availability and compliance of patients. Pulse therapy with Intra-Venous (i.v.) methylprednisolone followed by oral Prednisolone, and i.v. cyclophosphamide has not been

beneficial in FSGS but is promising in patients with MCNS and DMP. Immunosuppressive therapy plays a significant role in inducing long-term remission in SRNS and histopathology in SRNS is important to prognosticate.[10]

Eating, Diet, and Nutrition have not been shown to play a role in causing or preventing Nephrotic syndrome. For children who have developed Nephrotic syndrome, limiting intake of dietary sodium, often from salt, and fluid may be recommended to help reduce edema. A diet low in saturated fat and cholesterol may also be recommended to help control hyper-lipid-emia. Also control of protein intake weather from plant or animal sources should be considered in the management course either in active phase or after it to replace the amount lost during the course of the disease**.**[16]

Dietary factors

Sodium intake should imperatively be reduced to less than 6 g/day in order to minimize oedema and hypertension, and to potentiate the effect of ACE inhibitors and ARBs. Protein intake has been a subject of debate in Nephrotic syndrome. Various studies have demonstrated that a high protein diet (to correct for the urinary losses) per se was ineffective in correcting hypoalbuminemia.

Moreover, the increased protein intake tends to further increase protein-uria and glomerular hyper-filtration, and is therefore probably deleterious. Conversely, low protein diets (<0.8 g/kg/d) have a slight anti-protein-uric effect which might be valuable. Vegetable and fish proteins appear to be beneficial compared to animal proteins, and a low protein intake diet increasing the risk of malnutrition. Intravenous supplementation of albumin is not beneficial and is not recommended, except in cases of profound hypovolemia. A nutritionist consultation is recommended to every Nephrotic patient.[23]

Most patients with steroid sensitive Nephrotic syndrome (SSNS) have frequent relapses until disease resolve spontaneously toward the end of second decade of life. In children most common variety is minimal changes disease (MCD) characterized by response (sensitive), to steroid therapy.

So we must encourage & enforce the patient for regular medication taken, regular & long term follow up. And patient with family history of NS and had late response to steroid must be treated for long period to decrease the incidence frequent relapses.[24]

Children who fail to response to oral every other day steroid (EODS) may be treated with high dose intravenous methylprednisolone or with immunosuppressive agents such as cyclophosphamide, chlorambucil or cyclosporine A as a combination of these drugs or as isolated with different results. However SRNS may remit spontaneously or following courses of steroid longer than the standard 2 months**.** Other modality of treatment including azathioprine, Plasmapheresis, Low Density Lipoprotein aphaeresis, tacrolimus, vincristin, other non-immunosuppressive agent including angiotensin converting enzyme inhibitors (ACEI)**,** non-steroidal anti inflammatory drug and tuna fish oil.[25]

Nephrotic syndrome is a potentially chronic disease with patients suffering a relapsing course and being at risk of frequent courses of Prednisolone therapy with increase the risk of growth delay especially in patients reaching pubertal age and still taking steroid therapy. This leaves only the effects of the glucocorticoid treatment, which alters growth by.

1. Inhibition of Growth Hormone (GH) release.
2. Inhibition of Insulin-Like Growth Factor (IGF-I).

In steroid sensitive Nephrotic patients, the prolong course of the disease with increase number of relapses that expose the patient to more steroid and increase the risk of steroid toxicity, were have a significant rule in delaying the statural growth. Adolescent patients appear to be more affected during puberty[26].

Pharmacology[27]

NS Caused by Side effects of

1. Aminosalicylates for Ulcerative Colitis, & Crohn`s (Sulfasalazine, mesalazine, balsalazide, Olsalazine Sodium).
2. Dried Human Prothrombin Complex for pre-op prevention of congenital factors deficiency haemorrhage.
3. Immunosuppressant (Sirolimus).
4. Metabolic disorders Wilson’s disease (Penicillamine).
5. Nephropathic Cystinosis Mercaptamine (Cysteamine).

Indicated for Treatment of NS (1st line drugs) according to Fig. 4 & 5 .

1. Glucocorticoid therapy (Corticosteroid) like Prednisolone Deflazacort Sparing Agents.
2. **Alkylating** drugs (**Cyclophosphamide**)

3. **Immunosuppressant** calcineurin inhibitor Ciclosporin (**cyclosporin**) & **Tacrolimus** (nephrotoxic with aciclovir, amino-glycosides, amphotericin, Non-Steroidal Anti Inflammatory Drug, vancomycin), ₩ steroid caution in uncontrolled Hyper-Tension, uncontrolled infections, and cancer; in long-term Management, perform renal biopsies every 1–2 years.

4. Anti-proliferative **Immunosuppressant** Drugs affecting the immune response **Mycophenolate Mofetil**, Azathioprine, mercaptopurine, or once weekly methotrexate

5. Immunosuppressant (indometacin) Congenital NS.

6. **Antihelmintic** Immunomodulator (Ascaricides) **Levamisole**

7. Chimeric monoclonal antibody against CD20 **Rituximab**

Other or 2nd line managements in Resistance cases:

1. Human Albumin Solution
2. Potassium-sparing diuretics and aldosterone antagonists (Spirenolactone).
3. Oral potassium
4. Lipid-regulating drugs (Statins) atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin
5. Pneumococcal vaccines

Drugs used with cautions

1. Thiazides diuretics Chlortalidone
2. Alkylating drugs (Chlorambucil) may cause seizure, leukopenia & infections risk & not licensed for use.

Contraindicated drugs

1. Bile acid sequestrants Bezafibrate Treatment of hyper-cholesterol-emia

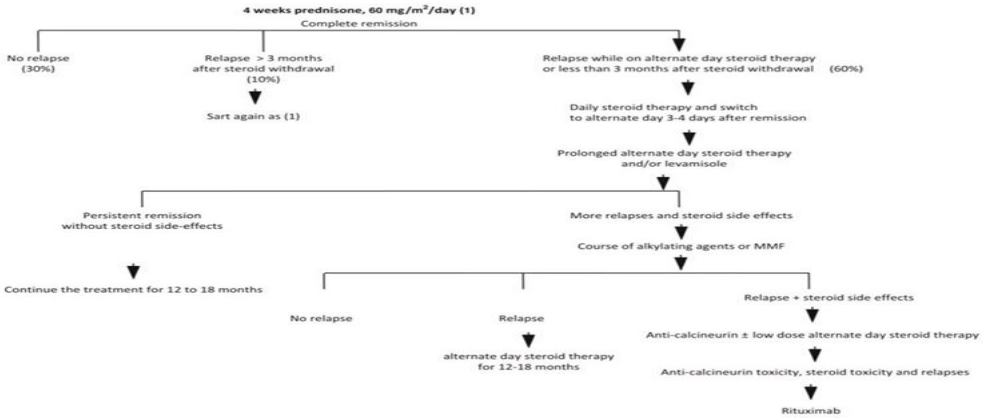

Fig. 4 Proposed algorithm for the treatment of steroid-dependent idiopathic nephrotic syndrome

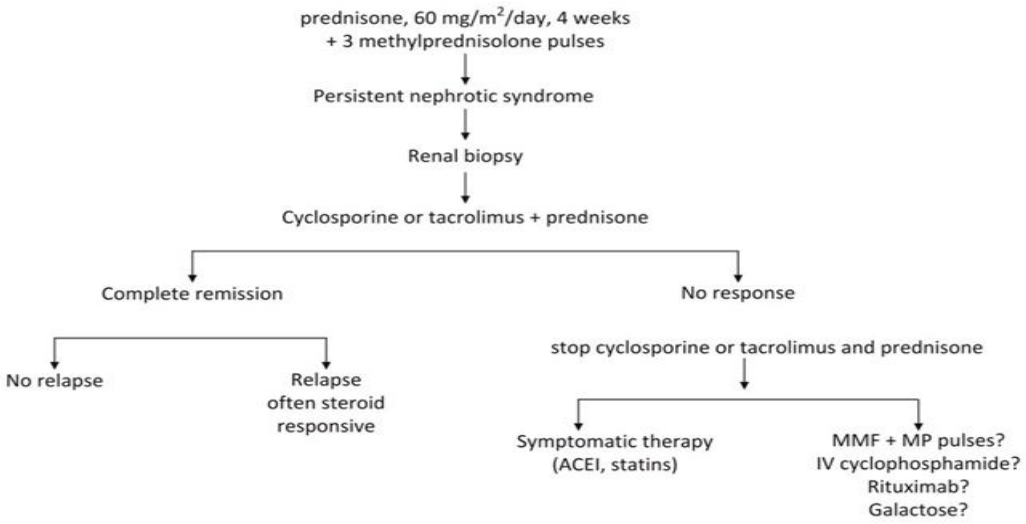

Fig. 5 Proposed algorithm for the treatment of steroid-resistant idiopathic nephrotic syndrome

AIM OF THE STUDY

The aim of this study is to review cases of N. S. in our hospital, to have a better understanding of epidemiological data, mode of presentation, response to treatment and complication.

PATIENTS AND METHODS

This Case Series study was undertaken at the Department of Pediatric, of Teaching Hospital in Sulaymaniyah, during the period 1st January of 2015 to the end of October of 2015 to revise N.S. in our city, and was followed up in the pediatric consultation clinic Family approval was taken by oral agreement from all parents of patients included in this study after explaining the benefits of informations and the research purpose. The study was carried out on families with patients age were between 6 months.-18 years. Children with NS who were diagnosed &/or treated in this hospital, were included in this study.

The data collected and recorded include the following information (age, gender, date of diagnosis, initial episode, type of presentation, positive family history of N.S., clinical presentation and investigation biochemical findings (blood urea, serum creatinine, total serum protein, serum albumin), treatment taken such as steroid, main specific 2nd line of management and other supportive drugs. Number of relapse and the time of each relapse, time needed to responds to & duration of steroid therapy and complication). We compared between frequent and infrequent groups regarding to age, sex, type of presentation, biochemical findings, precipitating factors, family history of renal disease, the time needed to respond to steroid therapy and duration of steroid therapy.

Patients with systemic illness such as systemic lupus erythematous, Glomerulonephritis & Noonan syndrome considered as secondary NS, and we didn't find other secondary cause such as henoch-schonlen purpura, sickle cell anemia, malignancies, metabolic disorders or hepatitis. And patients not eligible excluded from the study.

From this information, our patients were divided into 3 groups

1- Steroid sensitive N.S. (SSNS)

2- Steroid dependence N.S. (SDNS)

3- Steroid resistance N.S. (SRNS).

The steroid sensitive were divided into subgroups according to useful definition

1-Undetermined N.S.: first-time diagnosed and response to steroid therapy but they still on alternative day or complete therapy but not more than 6 month.

2-Frequent relapse N.S. (FRNS): two or more relapse per 6 months after remission from 1st attack, or 4 or more relapses within any whole year.

3-Infrequent relapse N.S. (IFRNS): less than 2 attacks of relapse within 6 months of 1st attack or less than 4 relapses per any year thereafter.

An interview method was used by the researcher to full constructive questionnaire format.

Statistical Analysis and data management

Data collected were analyzed statistically and performed using the available computer-based software Statistical Package for Social Science (SPSS version 21) was used for entry and analysis through computer.

The data results then presented as simple measures of number or percentage with use of Chi-square test (X2) for testing significance of statistical difference between different parameter and compare between proportion of study groups as number of percentage likelihood ratio test used to test the relations and compare proportions of different factors. With use of probability P value of < 0.05 was regarded as the level of statistically significance. Bar and Pie charts used to represent the data.

RESULTS

1. Sex

The male patients in this study were 10 (59%) and the female were 7 (41%). and the male to female ratio was ♂:♀= 1.4:1 as shown in table 2 and figure 6.

Table. 2: the Distribution of sex.

Sex	Frequency	Percent from the total No. of the pat (17)
Male	10	59%
Female	7	41%
Total	17	100%

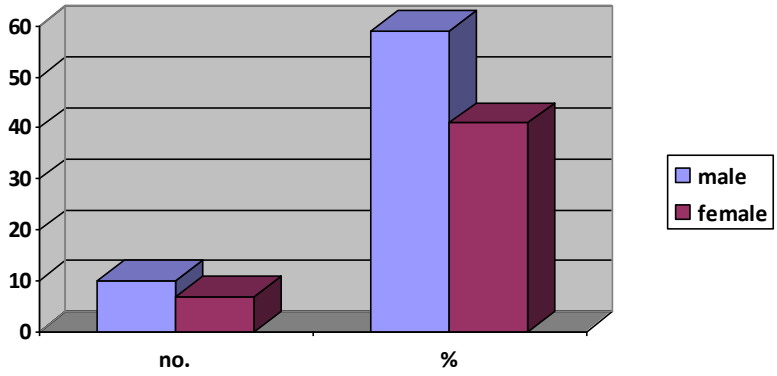

Figure. 6: the male to female ratio.

2. *Age & Age at diagnosis, socioeconomic status, Family History.*

The most frequent age group was 5-11 years. In 9 (52.9%), the age at diagnosis was 3-5 years, socioeconomic status according to income basis decided from the history taken, of the most patients was low 11 (64.7%), family history was negative among 13 (76.5%), while it was positive related to father among 2 (11.8%), and sister 2 (11.8%), as shown in table 3.

Table. 3: The general characteristics of the NS cases.

variables		Frequency	Percent
Age	< 5	5	29.4
	5-11	9	52.9
	> 11	3	17.6
Age at diagnosis	< 3 year	3	17.6
	3-5 year	9	52.9
	> 5years	5	29.4
Socioeconomic status	low	11	64.7
	Middle	6	35.3
	High	0	0
Family History	Negative	13	76.5
	Father	2	11.8
	sister	2	11.8
	Total	17	100.0

3. Other presentations or history findings,

The most frequent clinical feature was Odema in all of the cases, then fatigue 13 (76.5%), followed by abdominal Pain 12 (70.6%), and 7 patients (41.2) develop poor appetite and diarrhea respectively as shown in table 4.

Table. 4: The other clinical features.

Other features	Frequency	Percent from the total No. of the pat (17)
Odema	17	100
Fatigue	13	76.5
Abdominal Pain	12	70.6
Poor Appetite	7	41.2
Diarrhea	7	41.2
history findings		
Bee sting	2	11.8
Atopy	1	5.9

4. Blood Pressure changes

Regarding Blood Pressure changes, this was measured by myself using mercury sphygmomanometer in sitting position and compare with what the relative give a history of previous measures in every visit. It was high before treatment in 9 (52.9%), remained normal among 6 (35.5%), and increased as one of the complications after Treatment in 2 (11.8%), as shown in figure 7.

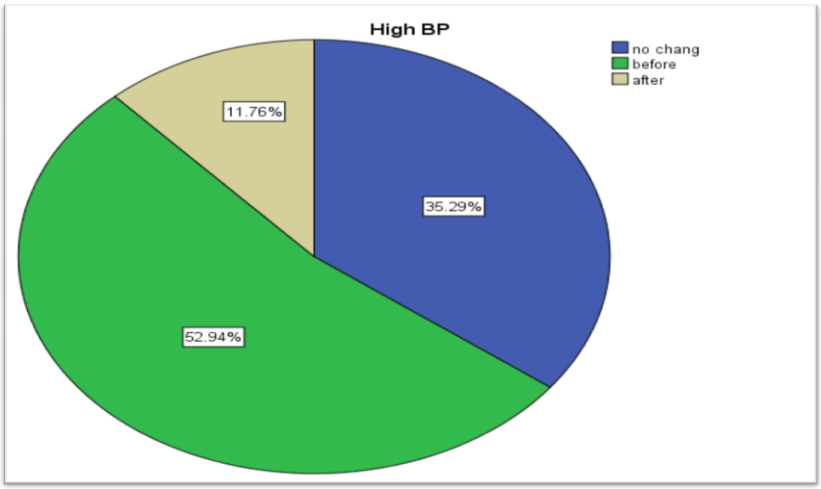

Figure. 7: the high Blood Pressure among NS pat.

5. *Cause:* Most of the NS cases were idiopathic 14 (82.4%), followed by secondary 3 (17.6%) which were previously diagnosed as systemic lupus erythematous, Glomerulonephritis & Noonan syndrome, as shown in figure 8.

Figure. 8: The distribution of the NS pat.

6. *Renal biopsy:* According to cause: Renal biopsy not done for 11 (64.7%), was MCNS 3 (17.6%), and FSGS in 3 (17.6%), as shown in figure 9.

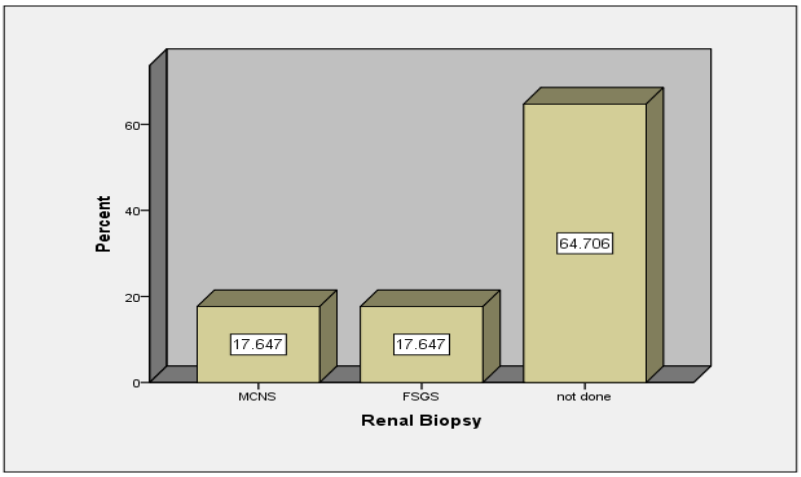

Figure. 9: the distribution of the NS according to the renal biopsy results.

7. Response to steroid & duration of it, Dependant, Relapses & its frequency

Although our study was 11 months duration, and because of the cases that previously diagnosed and treated with steroid for a period of time, they show response to steroid treatment among 9 (52.9%) of the patients. Steroid dependent cases were 6 (35.3%), and steroid resistance were 2 (11.8%). Most, 7 (41.2%) of the relapsing cases relapsed for < 4 times. Response occurred within 2 weeks in 10 patients (58.8%), as shown in table 5.

Table. 5: Major line of the treatment of the NS pat.

Treatment			Frequency	Percent from the total No. of the pat (17)
Steroid	SSNS	Response	9	52.9
	SDNS	Dependant	6	35.3
	SRNS	Resistant	2	11.8
Total			17	100
Duration till Response		2 w	10	58.8
		4w	3	17.6
		6w	1	5.9
		No	3	17.6
Total			17	100
Relapse/year		No	3	17.6
		less 4	7	41.2
		5-9	5	29.4
		more 9	2	11.8
Total			17	100

8. Lines of Management

All our patients received steroid, but some of them did not respond while others were dependant or resistant. So they needed 2nd line of management. Most frequently used drug from main specific group was MM IS 2 cases (11.8%), while, in the others sportive category Diuretics 11 (64.7%) followed by ACE inh 4 (23.5%) as shown in table 6, and Albumin was used in 13 patients (76.5%) as treatment of severe edema. Some take mixed Management.

Table. 6: other treatment lines used in the management.

Other Treatment lines used	Frequency	Percent from the total No. of the pat (17)
MM IS	2	11.8
Methyl Prednisolon	1	5.9
CPM	1	5.9
CS-A	1	5.9
Diuretics	11	64.7
ACE inh	4	23.5
Albumin	13	76.5
Aspirin	3	17.6
Statins	2	11.8
Pneumococcal Vaccine	2	11.8
Flu v.	1	5.9
Plasma	1	5.9
Total	17	100

9. *Complications, Infections types if occur, & Death:* Most frequent complication was pneumonia 9 (52.9%), followed by UTI 6 (35.3%), as shown in table 7. They are either cause or consequences of relapse.

Table. 7: the complications found among NS pat.

Complications	Frequency	Percent from the total No. of the pat (17)
Pneumonia	9	52.9
UTI	6	35.3
Anemia	3	17.6
Hematuria	2	11.8
ARF	1	5.9
Septicemia	1	5.9
Death	2	11.8

The distribution of the sample according to renal biopsy and the cause revealed that most of the idiopathic cases had biopsy results of MCNS 3(17.6%), and most of the secondary to systemic lupus erythematous, Glomerulonephritis & Noonan syndrome as mentioned previously, was FSGS 2(11.8%); this relation statistically was not significant, as shown in table 8.

Table. 8: The distribution of the sample according to renal biopsy and the cause.

Cause		Renal Biopsy		Total
		MCNS	FSGS	
idiopathic	No.	3	2	5
	%	17.6	11.8	29.4
2ndry	No.	0	1	1
	%	0	5.9	5.9
Total	No.	3	3	6
	%	17.6	17.6	35.3

Likelihood Ratio= 1.59, DF=2, p value > 0.05 NS

The distribution of the sample according to renal biopsy and the steroid treatment revealed that most of MCNS cases was steroid dependent 3 (17.6%), and of the FSGS was equal in respond, resistant, and dependent, each one of them (5.9%), this relation statistically was not significant, as shown in table 9 and figure 10.

Table. 9: The distribution of the sample according to renal biopsy and the steroid treatment.

Steroid		Renal Biopsy			Total
		MCNS	FSGS	not done	
Responsive	No.	0	1	8	9
	%	0	5.9	47.1	52.9
Resistant	No.	0	1	1*	2
	%	0	5.9	5.9	11.8
Dependant	No.	3	1	2*	6

	%	17.6	5.9	11.8	35.3
Total	No.	3	3	11	17
	%	17.6	17.6	64.7	100

* These cases indicated for and they should undergo renal biopsy as soon as possible.

Likelihood Ratio= 9.2, DF=4, p value > 0.05 NS

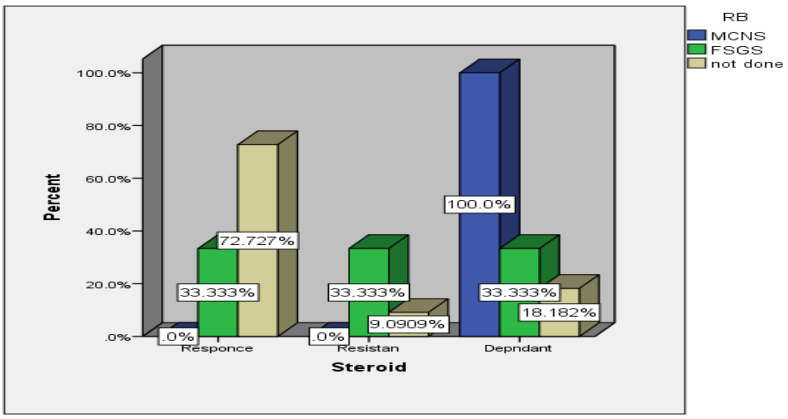

Figure. 10: The distribution of the sample according to renal biopsy and the steroid treatment.

The distribution of the sample according to renal biopsy and the relapse, revealed that most of MCNS cases had 5-9 relapses 2(66.7%), and of the FSGS was equal < 4 times 2 (66.7%),this relation statistically was not significant, as shown in table 10.

Table. 10: The distribution of the sample according to renal biopsy and the relapse.

Relapse			Renal Biopsy			Total
			MCNS	FSGS	not done	
	No	No.	0	0	3	3
		%	0	0	17.6	17.6
	less 4	No.	1	2	4	7
		%	5.9	11.8	23.5	41.2
	5-9	No.	2	1	2	5
		%	11.8	5.9	11.8	29.4
	more 9	No.	0	0	2	2
		%	0	0	11.8	11.8
Total		No.	3	3	11	17
		%	17.6	17.6	64.7	100

Likelihood Ratio= 6.46, DF=6, p value > 0.05 NS

The distribution of the sample according to steroid treatment and the relapse, which mean edema not protein urea, revealed that most of responded cases had <4 relapses 5 (29.4%), and all 2 (11.8%) of the resistant cases was between 5-9 times relapses, this relation statistically was significant, as shown in table 11.

Table. 11: The distribution of the sample according to steroid treatment and the relapse.

Relapse		Steroid			Total
		Response	Resistant	Dependant	
No	No.	3	0	0	3
	%	17.6	0	0	17.6
less 4	No.	5	0	2	7
	%	29.4	0	11.8	41.2
5-9	No.	0	2	3	5
	%	0	11.8	17.6	29.4
more 9	No.	1	0	1	2
	%	5.9	0	5.9	11.8
Total	No.	9	2	6	17
	%	52.9	11.8	35.3	100

Likelihood Ratio= 14. 621, DF=6, p value < 0.05 S

DISCUSSION

Nephrotic syndrome remains a major cause of referral to pediatric nephrologists because of the chronicity of the disorder and the complexity of its evaluation. However in our series study all of the children cases were diagnosed by symptoms appearance not by check up nor by accidently. With the number of children who were lost for follow-up skews findings particularly in the results.

1. *Sex:* In our study, which included 17 patients aged (1-18) years; we found that there has been gender preponderance of male children with male to female ratio approximately 1.4: 1. Table (2) & figure (4) show that male children are more affected than females. It has been emphasized that NS occur in boys more than girls in Baghdad pediatrics hospitals by Feryal et al.[13]

Consistent with epidemiologic findings in which NS is twice as prevalent in males and boys are affected more than girls which consistent with other studies like Kasim et al[24] and Nahla et al[19] both in Baghdad with 1.8:1 ratio and also nearly by Abdul-Kareem et al in Tikrit and Beji[10], Salim et al[26] in Baghdad as 1.6:1 and 2:1 respectively. The sex variation was statistically significant and so the sex is a good predictor factor in Peers because its agree with what mentioned in most of the books and researches.

2. *Age & Age at diagnosis*

The mean children`s age of presentation over the recent years was smaller while patients had an older age at presentation in contrast than before as Taghreed et al.[22]

In our study we found through table (3) that the main age group of diagnosis which was between 3-5 years and the presentation which was range between 5–10 years, It has been agreed what mentioned by Feryal et al study which state that "NS disease occurs at all ages, but most commonly between 2 and 5 years".[13]

Our finding comes against Kasim et al which said that around (80%) of cases of NS are almost present in preschool children and in relation to the onset of NS, but this study revealed that children at the age of 4 years and above and under 2 years are more affected may be explained by regional variation.[24]

3. *Socioeconomic status (SES)*

Importantly, the most occurrence of NS is at Low SocioEconomic Status (SES) 11 (64.7%), and the rest with middle SES. This is in contrast to the paucity of cases reported with high SES may be because due to small number of patients and the way of seeking medical help as distilled that the High SES most of the time go to private clinics, which are not included in our study case collection.

4. *Family History*

The study showed norm of that the family history of renal disease is a poor predictor. This is in contrast to deferent of the claims made by various studies particularly in study done by Kasim et al; they conclude that familial Nephrotic syndrome related to histopathology and steroid response.[24]

Contrastingly, our results show that 13 cases (76.5%) had no Family History and 4 cases (23.6%) with either father or sister diagnosed. Pertinently, in relation to family's heredity diseases, the result revealed that most children have no family history of diseases related to Nephrotic syndrome. This result agreed with another study which mentioned that "family history present usually in 3.5% of parent's" as demonstrated by Feryal et al.[13]

5. *Edema:* Also we can see the type of presentation was mainly periorbital edema but not anasarca (generalized massive SC tissue edema), which was present in most of the patients, then lower limbs, ascites, and both plural and genetalia, and it was the main presenting feature for all the sub groups. But all types of presentation were not similar to previous study done by Kasim et al.[24]

6. *Other presentations*

Table 4 show the most frequent clinical feature was fatigue 13 (76.5%), followed by abdominal Pain 12 (70.6%), then both poor appetite and diarrhea count 7 (41.2%). There is no similar reported study in pediatric population from Iraq showing a relation between atopy and bee sting with NS. Citing our result show only 2 (11.8%) had History of Bee Sting and only one patient (5.9%) engender Atopy. Children with Nephrotic syndrome (NS) undergo the same influences as the general population stated by Salim et al.[26]

7. *Blood Pressure changes*

As shown in figure 5, we find that 9 cases (52.9%) develop Hyper-Tension before treatment and 6 (35.5%) had no change in Blood Pressure and lastly 2 (11.8%) express an increase in Blood Pressure as one of the complications suggesting that hypertension was found in patients with relapse and long time treatment with steroid. In this study 11 patients (64.7%) were hypertensive a figure more than that found in patients of Nahla et al[19] with relapse and long time treatment with steroid which reported (39.4%), and higher than Iranian and Jordanian patients who reported (15.6%) and (14.28%) hypertensive patients respectively. Hypertension was more common for primary Nephrotic syndrome than that described by Abdul-Kareem et al (23.5%).[10]

8. *Cause*

In figure (6), Fourteen (82.4%) of our cases had INS, The rest 3 (17.6%) undergo 2ndry cause like Systemic Lupus Erythematosus and infection (septicemia & post Glomerulonephritis) this observation is similar to previous reports from different parts of the world. Previous studies Taghreed et al suggested that it could be secondary to environmental factors including infectious factors related to viruses, chemical exposure or many factors together. Genetic background could play a big role as coped before.[22] It has been mentioned in Feryal et al that "NS can be classified as primary when the syndrome is restricted to glomerular injury, or secondary when it develops as a part of systemic illness".[13]

9. *Renal biopsy*

We found that the procedure applied to six patients (35.3%) which divided equally between MCNS & FSGS, while the rest 11 (64.7%) didn't perform it. The typically featured patient are considered as MCNS so renal biopsy is not indicated and the rest who undergo the procedure seemed to be MCNS & FSGS types of NS and the majority of children in this study have no renal biopsy agreed with the guidelines and what mentioned that "pre-

adolescents who have NS without nephritis sings, hypocomplementemia or signs of systemic disease do not need a kidney biopsy before the initiation of therapy as in Feryal et al.[13]

Similar to the authors in the other series, we were careful to exclude any known secondary etiology and believe that there is a true universal increase in the incidence. We have found an incidence of MCNS & FSGS in children presented with I.N.S. in our period of our study; our results showed that FSGS was equally common histopathological-subtype in our patients who underwent renal biopsy during the study period. The increased incidence of FSGS in our study is in agreement with that reported in pediatric population from other studies applied in different countries. If we assumed that all patients that were not biopsied had minimal change disease (MCD) (presumptive MCD), the total incidence of MCNS (presumptive MCD + biopsy proven) was lower than anticipated, although we apply our study in different locality to compare with other studies. That FSGS was a rare cause of nephrosis in children in our study, which observed in Taghreed et al only 5.3%. And N.S. with increasing incidence of FSGS during the last decade, accompanied by significant decline in the incidence of MCNS. And she found a higher incidence of FSGS in children with reciprocal decline in the incidence of MCD in recent years.[22]

However, they reported high prevalence of FSGS 39% in biopsies in their finding support the nation that there is a global trend of increasing FSGS incidence in childhood N.S. MPGN is a rare cause of childhood I.N.S She, Taghreed et al, conclude that there is a shift toward an increasing incidence of FSGS and to lesser extent, the MPGN in Iraqi children presenting with I.N.S. This changing trend of histopathological patterns has profound prognostic significance and has significant implications in the management of childhood Nephrotic syndrome.[22] Our finding is in agreement with performing renal biopsies on children with I.N.S. who are steroid dependant in addition to those who are steroid resistant particularly before starting cytotoxic medication. This approach will be beneficial in the management of those patients and it will help to solve the mysteries of the disease process involved.

10. *Response to steroid & duration of it,*

This study showed that the main type of NS is SSNS 9 (52.9%) followed by SDNS 6 (35.3%) then SRNS 2 (11.8%) as seen in table 6. These results similar to previous studies by Kasim et al. Regarding the time needed to responds to steroid therapy, most patients showed an early response to treatment during the 1st two weeks after starting the treatment.

So 51(60%) patients with SSNS responded between 2 – 4 weeks and 24(28%) patients responded > 4 weeks, and with statistically difference between Frequent Relapse & InFrequent Relapse, this was result of studies done by Kasim et al which concluded that there is evidence that the liability to subsequent relapse of SSNS is influenced by both the intensity and the duration of initial corticosteroid regimen.

The duration of treatment doesn't show any statistically significant difference between Frequent Relapse & InFrequent Relapse and this is not similar to previous study done by Kasim et al, and this may be due to irregular follow up of patients and inadequate adherent to medication by patients or their parents.[24]

After initiation of steroid therapy, in most cases the protein losses regress quickly. This leaves only the effects of the glucocorticoid treatment. This consistent with previous studies Salim et al, which suggest that longer steroid treatment with higher cumulative doses of Prednisolone, was also the paramount cause of complications in children with early onset Nephrotic syndrome.[26]

Also we found that mothers do not interrupt therapy without doctor advice; this result is in constant with Feryal et al study which emphasized that the drug should be continued until the urine is free from protein and becomes normal, and the parent should know that therapy is to be continued according to the limited schedule and limited dose until urine becomes free of protein-uria.[13]

11. *Dependant, Relapses & its frequency:* Steroid therapy was given to all patients with initial attack and relapses. Steroid sensitive NS was found in 15 cases (88.2%). High prevalence of SSNS also found in contrasts with earlier reports of Nahla et al from other parts of Iraq where poor response to steroid therapy was common.[19]

The variation or comparing between Frequent Relapse & InFrequent Relapse patients in regarding to age of presentation show in our result statistically not significant and so these result differ from previous first study done by Kasim et al, which mentioned that the early onset NS associated with frequent relapses[24]. It has been recommended that the patients should receive up to 6 months of prednisone before determining that the patients have SRNS. So our result with its simplicity can be supported by second study done by Kasim et al study.[25]

12. ***Other lines of Management***

The need for many therapeutic trials for SRNS indicates that final word has not been said by Abdul-Kareem et al which mean every doctor – patient should decide their approach accordingly.[10]

The use of alternative therapy (alkylating agents e.g.; cyclophosphamide or cyclosporine A or others) should be considered, in particular during periods of higher risk for SRNS stated by Salim et al from the experience of trying them.[26]

No generally accepted treatment regimen is available for patients with SRNS. For this reason, a numbers of studies have been performed with immunosuppressive intervention as steroid (EODS, Methyl Prednisolone), CPM, chlorambucil CS-A, Tacrolimus and Plasmapheresis or immunoadsorpant according to Kasim et al which applied on multiple drug types receivers. But there is no clear cut evidence in favor of any kind of treatment for each patient because each one is unique, like Methyl Prednisolone and sometimes triple therapy of Methyl Prednisolone, with EODS, +/- alkylating agents.[25]

The result of this study was affected by two factors, the availability of medication and equipment and the compliance of the patients and the family. Medication used as shown in table 6 is the common one as an option of treatment but our results affected by the small numbers of patients. The reason of that mostly related to compliance of patients because the patients must come and admitted to the hospital for few days to weeks, the second reason could be the availability of the drugs to that reason Kasim et al provide strong evidence of benefit of commitment.[25]

In table 6, we found that only 2 (11.8%) treated by MM IS, from the main line of managing, and 13 (76.5%) use Albumin, 11 (64.7%) prescribed diuretics for them, 4 (17%) indicated for ACEi for Hyper-Tension, Lipid-Regulating Drugs (Statins) & Pneumococcal Vaccine.

Lastly one patient only (5.9%) takes CS-a, CPM & Methyl Prednisolon, flu v., and Plasma. In Feryal et al, mothers who allow their children to act actively. This agreed with state that "Bed rest does not need to be enforced".[13]

13. ***Side effects***

Our patients had sign of steroid toxicity in form of cushingoid features with or without hypertension and/or obesity, several authors, have argued that prolonged alternate-day steroid

treatment cause a lot of side effects in Nephrotic patients. This consistent with that in Salim et al study which concludes that prolonged steroid therapy in frequent relapsing Nephrotic syndrome may produce moon face and other distressing side effects.[26]

The findings of the study pointed out that majority of patients observe the side effects of therapy, especially corticosteroid. This result does not agree with the study, Feryal et al, which reported that the side effects of steroid-therapy is lower than expected while the child receiving it. This finding revealed mothers worries about child's condition or due to poor information that mothers have about the side effects of steroid-therapy.[13]

14. *Infections types if occur:* Infections are the most complication seen in NS patients according to our study, Pneumonia, UTI show the occurrence of 9 (52.9%), & 6 (35.3%) respectively, also they may be precipitating factor for relapses. In regard to the protection of child from getting diseases, mothers sometimes protect their children from getting respiratory tract infection. Children with NS have decreased immunity and are highly susceptible to infection; mothers never take doctor re-assurance of giving vaccine in account. This result agrees with Feryal et al study which mentions that the mother does not know the contraindication of the vaccine on chronic disease, such as kidney diseases. It has been emphasized that live vaccine is contraindicated in children with NS on daily corticosteroid therapy.[13]

15. *Complications*

Anemia 3 (17.6%), and Hematuria 2 (11.8%) were less common than that described for primary Nephrotic syndrome. This is contrary to the study done by Abdul-Kareem et al.[10]
Each one case (5.9%) had either renal failure, Arthritis, Septicemia, or Hepatosplenomegaly.

16. *Death*

Which may be due to various reasons; unfortunately two children (11.8%) had died before 3rd year of life due to septicemia, nearly the same percentage result of Abdul-Kareem et al.[10]

CONCLUSION

1. There is an equal incidence in the frequency of MCNS and the FSGS in our study.
2. Diagnosis and follow up of Nephrotic patients require close cooperation between general practitioners and nephrologists. Evaluation and treatment of complications are crucial to minimize the mortality and morbidity.

3. A careful evaluation of Nephrotic patients is essential for optimal care and management.
4. Further large studies are needed in Iraq to find out changing trends of histopathology in childhood Nephrotic syndrome.
5. The frequency of hypertension in steroid resistant Nephrotic syndrome is higher than that of steroid sensitive and steroid dependent.
6. Mothers should protect their children from infection such as flu and respiratory tract infection due to loss of immunoglobulin in the urine.
7. Lastly, Ultrasound-guided percutaneous renal biopsy is a safe procedure in the diagnosis of parenchymal kidney diseases.

RECOMMENDATIONS

1. It is the responsibility of Health Ministry to encourage pediatricians to have subspecialty in pediatric nephrology & open a unit in each pediatric hospital with stuff of doctors and nurses, put guide lines pamphlets for them, and train them to diagnose new cases and follow up old ones; renal biopsy facilities must be available in hospitals. We should insist on proper documentation in the patient's record & improve the laboratory work.
2.Educate parents especially mothers to know how to deal with relapses, factors affecting the prognosis & the need to perform renal biopsy when indicated & other drugs with knowledge to their advantage & disadvantage, by printing a leaflets in simple Kurdish & Arabic language.
3. Encourage & enforce the families for re-evaluation by routine examination of Wight, growth assessment, Blood Pressure monitoring and urine & blood analysis with psychological support accordingly every certain period of time, let us say monthly.
4. The mass media should do their roles in educative progress that explain the disease in a simple manner.

Limitations

1. Small sample size.
2. Short duration of study i.e. we couldn't follow up cases for longer time.
3. Absence of specialized unit to control.
4. The new lines of management, we have no experience with applying them, and sufficient studies to prove their benefit.
5. Poor compliance of the parents in both presenting old informations and follow up.

REFERENCES

1. Mahdi Sahib Abueed, Childhood NS and Frequency of Hyper-Tension, Baghdad, Iraqi board for the medical specialization in pediatrics, 2008.
2. Chester M Edelmann Jr., Clinical-pathological correlations in the N.S., Pediatric Research, Einstein Coll. Med., N.Y.2013.
3. Chris Clardy, NS in Children, Pediatric all Nephrology Handout, May 2000.
4. Charles Kodner, NS Diagnosis and Management, American Family Physician, Vol. 80, No. 10, November 15, 2009.
5. Monir H. Naif, Clinicopathological Features of primary NS in Iraqi children, Iraqi Board of Pediatric Nephrology, 2012.
6. Gordillo R. and A Spitzer, NS in Pediatric Patients, Review American Academy of Pediatrics, 2009; 30(3): 94-104.
7. Nelson Textbook of Pediatrics, 20 Ed, 2016, ch 527 p2521.
8. Jerome C Lane, NS, Northwestern University Medical School, Children's Memorial Hospital, Chicago, emedicine.medscape.com, May 12, 2010.
9. Eric P Cohen, MD; Vecihi Batuman, MD, FACP, FASN, NS e-medicine.medscape 2013.
10. Abdul-Kareem M. Ali, Treatment of Steroid Resistant NS, University of AL- Nahrain, Iraqi J. Comm. Med., July, 22, 2009; 22(3).
11. Naaeem Salim Hashem, U.T.I. in Children with Idiopathic NS in Annajf Alasheraf city, Iraqi scientific council of pediatrics, College of Medicine, Kufa University, 2013.
12. Thulfigar Ibrahim Salih, Patients With positive Family History of NS, Iraqi Commission for Medical Specialization in Pediatrics. College of Medicine, University of Baghdad 2012.
13. Feryal A. Zyarah, Assessment of mothers' practices toward children with steroid – sensitive NS at pediatrics hospitals in Baghdad city, Iraqi National Journal of Nursing Specialties, 2011; 24(2): P24.
14. Nariman F. A.Azat, Evaluation of Serum (IgG, M) in children with NS relapse, Fac Med Baghdad, , 2012; 54(1).
15. Merck Manuals Online Medical Library. Nephrotic Syndrome. Updated March 2013. Accessed December 4, 2013.
16. Clearinghouse National Kidney and Urologic Diseases Information - NS up to date 2013.
17. Hamza Ibrahim Zain, NS in Childhood a Single Center Study, Iraqi Board for Medical Specialization, Mosul, 2010.
18. Mira T. Keddis, NS, Hospital Physician October, 2007; 25-30: 38.

19. Nahla I. A. l. Gabban, NS and Hyper-Tension, Iraqi J. Comm. Med., p 271-275, Oct. 2010.
20. Louis-Philippe Laurin, Contraindications Renal Biopsy, INTECH Topics, University of Montreal, Canada, 2012.
21. Muhammed Mubarak, Contraindications Renal Biopsy, Topics in Renal Biopsy and Pathology, (Ed.) 2011.
22. Taghreed Fadel Mohammed, Trends of Histopathology in Childhood NS, Iraqi Postgraduate Medical Journal, 2009; 1(1): 47-52.
23. Sophie de Seigneux, Management of patients with NS, Swiss Med Wkly, 2009; 139: (29–30): 416-422.
24. Kasim Rahi, Childhood NS, Frequent and Infrequent Relapses and Risk Factors for Relapses, The Iraqi Postgraduate Medical Journal, 2009; 8(3): 291-294.
25. Kasim Rahi Issa, Options of the Treatment in Steroid Resistant NS in Children in Central Child Teaching Hospital-Baghdad, The Iraqi Postgraduate Medical Journal, 2010; 9(3): 316-319.
26. Salim Zyara Abdullah, Growth Delay in Steroid Sensitive NS Patients, The Iraqi Postgraduate Medical Journal, 2007; 6(2): 129-134.
27. British National Formulary (BNF) for Children, 2015 C6.3.2 P.378.
28. Nariman F. Ahmed, Childhood NS clinical manifestations & histopathological spectrum, Fac Med Baghdad, 2007; 49(3): 304.
29. Faris M. Frankul, Hyper-Tension in children with NS, J Fac Med Baghdad, 2005; 47(1): p5.
30. NS guide, National Kidney and Urologic Diseases, Information Clearinghouse, March 2012.
31. Childhood NS guide, National Kidney and Urologic Diseases, Information Clearinghouse, August 2014.
32. Childhood NS parents guide, The Kidney Foundation of Canada, 2007.
33. Sitti Aizah Lawang, Plasma lipids as risk factors in relapsing Nephrotic syndrome, Paediatrica Indonesiana,v. 48, n. 6, p322, November 2008.
34. Sangita U. Sawant, Correlation between Oxidative Stress and Thyroid Function in Patients with Nephrotic Syndrome, International Journal of Nephrology, Article ID 256420, 2011.

35. Mona Khurana, Etiology and management of dyslipidemia in children with chronic kidney disease and end-stage renal disease, Pediatr Nephrol, Center for Drug Evaluation and Research Office, p2073, 2015.
36. Juan Jesus Carrero, Lipid disorders in chronic kidney disease: Reverse epidemiology and therapeutic approach, Journal of Nephrology Karolinska Institutet. v21, p635-644, November 2007.
37. Paul S. Jellinger, Mx of Dyslipidemia & Prevention of Atherosclerosis, American Association of Clinical Endocrinologists, v18 2012.
38. Brenner & Rector, Nephrotic Syndrome, MD Consult of Elsevier, 2004.
39. K. Kaarthigeyan, N. S. following a single bee sting in a child, Indian Journal of Nephrology, V. 22, No. 1, Jan-Feb, 2012, pp. 57-58.
40. Maher Abdel-Hafez, Idiopathic Nephrotic Syndrome and Atopy: Is There a Common Link?, American Journal of Kidney Diseases, 2009.
41. AbdelAziz Yousef Elzouki, Immunological aspects of primary nephrotic syndrome in childhood, Department of Pediatric Nephrology, Maternity and Children's Hospital, Riyadh, Saudi Arabia, 1994; v5, i4: 483-488.
42. Lawrence Copelovitch, Childhood Nephrotic Syndrome in Cambodia; An Association with Gastrointestinal Parasites, Journal of Pediatrics, Jan. 2010; 156(1): 76.
43. Chang-Ching Wei, Occurrence of Common Allergic Diseases in Children with Idiopathic Nephrotic Syndrome, J Epidemiol, 2015; 25(5): 370-377.
44. Chang-Ching Wei, Risk of idiopathic N. S. among children with asthma a nationwide, population-based cohort study, Pediatric Research, Nature Publishing Group, v78, i2, p212-217, 2015.