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Trigger Factors of Relapses In Children with Nephrotic Syndrome

A Research submitted to Al-Nahrain University /Collage of Medicine In Partial Fulfilment for the Degree of M.B.CH.B

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2019

Acknowledgments

I would like to give my deepest gratitude to every person who helped me to complete this research .

My grateful thank to my supervisor (***Dr.shatha Hussain***) for everything she did , still does and for her encouragement and her big help we couldn't have this without her

Finally special thanks to ***my family*** for their support

Dedication

To the person who always support and stand with me

My Father

To the person who made everything easy and possible

My Mother

My great thanks and respect to my supervisor

Dr.shatha Hussain

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Abstract

Background: Nephrotic syndrome (NS)is the clinical manifestation of glomerular diseases associated with heavy (nephrotic range)proteinuria >3.5\24hr or protein;creatinine ratio>2 .

Aim :Study the trigger factors of relapses in children with steroid sensitive nephrotic syndrome (SSNS).

Method Retrospective study at Al-Imamman Alkadimain Medical City from period 1\11\2018 to 20\1\2019.

Forty child with steroid sensitive nephrotic syndrome collected from the pediatric nephrology clinic . Data collected from the file records of patients

Results: Total number was 40 child with (SSNS) with 58 relapses .23 males (57.5%)and 17 females(42.5%), 13 (32.5)patients between 1-5y,18(45%) patients between 5-10y and 9(22.5%) patients above 10y , 24(60%) patients from urban areas while 16 (40%)patients from rural areas, 23 (57.5%)patients had frequent relapses while 17(42.5%) with infrequent relapses, the most common cause of relapses was infections (51) (88%) and the second cause of relapse was examination days .(3)(5.2%) , from the infections the UTI is the most common cause of relapse 31(53.5%) followed by URTI 15 (25.9%) .

Conclusion :frequent relapses > infrequent, infections is the most common cause of relapses followed by examinations ,UTI is the most common cause of relapse from infections , UTI cause more relapse in females while URTI cause more relapses in males

Recommendation : proper follow up of patients and early detection of relapses and proper management and good search for source of infection with relapse is indicated for treatment particularly UTI and URTI.

Introduction

- Nephrotic syndrome (NS) is the clinical manifestations of glomerular diseases associated with heavy (nephritic range) proteinuria

Nephrotic range proteinuria defined as :
Proteinuria >3.5g\24hr or urine protein ;creatinine ratio>2
Clinical finding associated with (NS) arising from the large urinary loss of protein , hypoalbuminemai (<2.5g\dl),edema and hyperlipidemai (chol >200mg\dl).
(NS) usually accompanied by sodium and water retention that may be little in amount only see in face (eyelids) or generalized involve lower limbs or all the body (anasarca).(1)

Epidemiology
(NS) affects 1-3 per 100,000 children <16yr of age
The annual incidence of NS in children in USA and Europe has been estimated to be 1-7 per 100,000 children , with a cumulative prevalence of 16 per 100,000 children .
Although it is mainly found in adults with ratio of adults to children 25:1
There is difference in epidemiology between the sexes, more common in males than females in ratio 2:1
Higher rates of (NS) reported in children of Arabian and Asian racial in contrast to Caucasian children.(2)

Definitions
Relapse :protein +ve on 3 consecutive days within 7 days plus edema
Frequent relapse NS :steroid sensitive NS with 2 or more relapses within 6m or more than 3 in one year
infrequent relapse NS :steroid sensitive NS with less than2 relapses within 6m (3)

Classification:

Nephrotic syndrome can be classified into three groups :-

· primary or idiopathic nephrotic syndrome(85-90%)

· secondary to systemic diseases such as systemic lupus erythematosus, Henoch-Schönlein purpura, malignancy
(lymphoma and leuke- mia), and infections (hepatitis, HIV, and malaria)(5-8%)

· Congenital nephrotic syndrome that begin before 6 months and may be caused by intrauterine infections like toxoplasmosis and hepatitis (very rare 1-2%) (1)

Pathogenesis

- Role of the Podocyte

The underlying abnormality in nephrotic syndrome is an increased permeability of the glomerular capillary wall, which leads to massive proteinuria and hypoalbuminemia. The podocyte plays a crucial role in the development of proteinuria and progression of glomeruloscle- rosis. The podocyte is a highly differentiated epithelial cell located on the outside of the glomerular capillary loop . Foot processes are extensions of the podocyte that terminate on the glomerular basement membrane. The foot processes of a podocyte interdigitate with those from adjacent podocytes and are connected by a slit called the slit diaphragm. The podocyte functions as structural support of the capillary loop, is a major component of the glomerular filtration barrier to proteins, and is involved in synthesis and repair of the glomerular basement membrane. The slit diaphragm is one of the major impediments to protein permeability across the glomerular cap- illary wall. Slit diaphragms are not simple passive filters—they consist of numerous proteins that contribute to complex signaling pathways and play an important role in podocyte function. Important compo- nent proteins of the slit diaphragm include nephrin, podocin, CD2AP, and α-actinin 4. Podocyte injury or genetic mutations of genes produc- ing podocyte proteins may cause nephrotic-range proteinuria (3)

In idiopathic, hereditary, and secondary forms of nephrotic syndrome, there are immune and nonimmune insults to the podocyte that lead to foot process effacement of the podocyte, a decrease in number of functional podocytes, and altered slit diaphragm integrity. The end result is increased protein “leakiness” across the glomerular capillary wall into the urinary space. (2)

· Role of the Immune System

Minimal change nephrotic syndrome (MCNS) may occur after viral infections and allergen challenges.That immunosuppression occurs with drugs such as corticosteroids and cyclosporine provides indirect additional evidence that the immune system contributes to the overall pathogenesis of the nephrotic syndrome. (1)

Pathophysiology

- Edema

Edema is the most common presenting symptom of children with nephrotic syndrome. Despite its almost universal presence, there is uncertainty as to the exact mechanism of edema formation. There are 2 opposing theories, the underfill hypothesis and the overfill hypothesis, that have been proposed as mechanisms causing nephrotic edema.(4)

· The underfill hypothesis is based on the fact that nephrotic-range proteinuria leads to a fall in the plasma protein level with a correspond- ing decrease in intravascular oncotic pressure. This leads to leakage of plasma water into the interstitium, generating edema. As a result of reduced intravascular volume, there is increased secretion of vasopressin and atrial natriuretic factor, which, along with aldosterone, result in increased sodium and water retention by the tubules. Sodium and water retention therefore occur as a consequence of intravascular volume depletion.(3)

This hypothesis does not fit the clinical picture of some patients with edema caused by nephrotic syndrome who have clinical signs of intra- vascular volume overload, not volume depletion. Treating these patients with albumin alone may not be sufficient to induce a diuresis without the concomitant use of diuretics. Also, reducing the renin–aldosterone axis with mineralocorticoid receptor antagonists does not result in a marked increase in sodium excretion. With the onset of remission of MCNS, many children will have increarased urine output before their urinary protein excretion is measurably reduced. (8)

· The overfill hypothesis postulates that nephrotic syndrome is associ- ated with primary sodium retention, with subsequent volume expan- sion and leakage of excess fluid into the interstitium. There is accumulating evidence that the epithelial sodium channel in the distal tubule may play a key role in sodium reabsorption in nephrotic syndrome. The clinical weaknesses of this hypothesis are evidenced by the numerous nephrotic patients who present with an obvious clinical picture of intravascular volume depletion: low blood pressure, tachy- cardia, and elevated hemoconcentration. Furthermore, amiloride, an epithelial sodium channel blocker, used alone is not sufficient to induce adequate diuresis. (5)

- Hyperlipidemia

There are several alterations in the lipid profile in children with nephrotic syndrome, including an increase in cholesterol, triglycerides, low-density lipoprotein, and very-low-density lipoproteins. The high- density lipoprotein level remains unchanged or is

low. In adults, this results in an increase in the adverse cardiovascular risk ratio, although the implications for children are not as serious, especially those with steroid-responsive nephrotic syndrome. Hyperlipidemia is thought to be the result of increased synthesis as as well as decreased catabolism of
lipids. Although commonplace in adults, the use of lipid-lowering agents in children is uncommon. (1,4,6)

- hypercoagulable

Nephrotic syndrome is a hypercoagulable state resulting from multiple factors: vascular stasis from hemoconcentration and intravascular volume depletion, increased platelet number and aggregability, and changes in coagulation factor levels. There is an increase in hepatic production of fibrinogen along with urinary losses of antithrombotic factors such as antithrombin III and protein S. Deep venous thrombo- sis may occur in any venous bed, including the cerebral venous sinus, renal vein, and pulmonary veins. The clinical risk is low in children (2-5%) compared to adults, but has the potential for serious consequences. (2,6,7)

Pathology of idiopathic nephrotic syndrome

- Idiopathic nephrotic syndrome includes multiple histologic types:
- minimal change nephrotic syndrome
- focal segmental glomerulosclerosis,
- membranoproliferative glomerulonephritis and
- mesangial proliferation

MCNS is present in 85-90% of patients <6 yr of age. In contrast, only 20-30% of adolescents who present for the first time with nephrotic syndrome have MCNS The more common cause of idiopathic nephrotic syndrome in this older age group is FSGS. The incidence of FSGS may be increasing; it may be more common in African-American, Hispanic, and Asian patients.

Minimal change nephrotic syndrome(MCNS)

(approximately 85% of total cases of nephrotic syndrome in children), the glomeruli appear normal or show a minimal increase in mesangial cells and matrix. Findings on immunofluorescence microscopy are typically negative, and electron microscopy simply reveals effacement of the epithelial cell foot processes. More than 95% of children with minimal change disease respond to corticosteroid therapy. (2)

Mesangial proliferation

is characterized by a diffuse increase in mesangial cells and matrix on light microscopy. Immunofluorescence microscopy might reveal trace to 1+ mesangial IgM and/or IgA stain- ing. Electron microscopy reveals increased numbers of mesangial cells and matrix as well as effacement of the epithelial cell foot processes. Approximately 50% of patients with this histologic lesion respond to corticosteroid therapy. (7,8)

Focal segmental glomerlosclerosis(FSGS)
glomeruli show lesions that are both focal (present only in a proportion of glomeruli) and segmental (localized to ≥1 intraglomerular tufts). The lesions consist of mesangial cell proliferation and segmental scarring on light microscopy. Immunofluorescence microscopy is positive for IgM and C3 staining in the areas of segmental sclerosis. Electron microscopy demonstrates segmental scarring of the glomerul tuft with obliteration of the glomerular capillary lumen. Similar lesions may be seen secondary to HIV infection, vesicoureteral reflux, and intravenous use of heroin and other drugs of abuse. Only 20% of patients with FSGS respond to prednisone. The disease is often progressive, ultimately involving all glomeruli, and ultimately leads to end-stage renal disease in most patients. (4,5)

Presentation of nephrotic syndrome

· The initial episode of idiopathic nephrotic syndrome, as well as subsequent relapses, usually follows minor infections and, uncommonly, reactions to insect bites, beestings, or poison ivy.

· Children usually present with mild edema, which is initially noted around the eyes and in the lower extremities.

· With time, the edema becomes generalized, with the development of ascites, pleural effusions, and genital edema. (5,6)

· Anorexia, irritability, abdominal pain, and diarrhea are common.

· Important features of minimal change idiopathic nephrotic syndrome are the absence of hypertension and gross hematuria (the so-called nephritic features).

· The differential diagnosis of the child with marked edema includes protein-losing enteropathy, hepatic failure, heart failure, acute or chronic glomerulonephritis, and protein malnutrition.

· A diagnosis other than MCNS should be considered in children <1 yr of age, with a positive family history of nephrotic syndrome, and/or the presence of extrarenal findings (e.g., arthritis, rash, anemia), hypertension or pulmonary edema, acute or chronic renal insufficiency, and gross hematuria. (2,3)

Diagnosis

- Urinalysis

- Show hematuria in 20% only
- 24hour total urine protein estimation more than (3,5g per liter per24 hour)
- early morning protein +3or+4 on dipstick
-spot creatinine protein ratio more than 2
- urine albumin excretion >40mg/m2 per hour

- Blood test

-serum albumin <2 g/ dL
- serum cholesterol >200 mg/dL
-also triglycerides may be elevated
- serum creatinine may be normal (may be abnormally elevated if there is diminished renal perfusion from contraction of the intravascular volume)

· Other investigations

evaluation to rule out secondary forms of nephrotic syndrome (children ≥10 yr): complement C3 level, antinuclear antibody, double-stranded DNA and hepatitides B and C, and HIV in high-risk populations

- Ultrasound to role out any anomalies

- Renal biopsy

is not routinely performed if the patient fits the standard clinical picture of MCNS.
Indications for renal biopsy
-Age of onset<1 year
-Gross hematuria,persistent microscopic hematuria or low C3
-sustained hypertension
-suspected secondary causes
- renal insufficiency with onset of the symptoms
After initial treatment
-proteinurea persists despite 4week of corticosteroids treatment .(1)(2)

· **Treatment**

Children with their first episode of nephrotic syndrome and mild to moderate edema may be managed as outpatients.

In children with presumed MCNS, prednisone or prednisolone should be administered as a single daily dose of 60 mg/m2/day or 2 mg/kg/day to a maximum of 60 mg daily for 4-6 wk followed by alternate-day prednisone (starting at 40 mg/m2 qod or 1.5 mg/kg qod) for a period ranging from 8 wk to 5 mo, with tapering of the dose. When planning the duration of steroid therapy, the side effects of prolonged cortico- steroid administration must be kept in mind. (6,7)

Approximately 80-90% of children respond to steroid therapy. Response is defined as the attainment of remission within the initial 4 wk of corticosteroid therapy. Remission consists of a urine protein : creatinine ratio of <0.2 or <1+ protein on urine dipstick for 3 consecutive days. The vast majority of children who respond to prednisone therapy do so within the first 5 wk of treatment. (2)

- Managing the Clinical Sequelae of Nephrotic Syndrome
- Edema.

Children with severe symptomatic edema, including large pleural effusions, ascites, or severe genital edema, should be hospitalized. In addition to sodium restriction (<1500 mg daily), water/fluid restriction may be necessary if the child is hyponatremic. A swollen scrotum may be elevated with pillows to enhance fluid removal by gravity. Diuresis may be augmented by the administration of loop diuretics (furosemide), orally or intravenously, although extreme caution should be exercised. Aggressive diuresis can lead to intravascular volume depletion and an increased risk for acute renal failure and intravascular thrombosis. (6,8)

- Dyslipidemia

Dyslipidemia should be managed with a low-fat diet. Dietary fat intake should be limited to <30% of calories with saturated fat intake <10% calories. Dietary cholesterol intake should be <300 mg/day. There are insufficient data to recommend the use of 3-hydroxy-3-methylgluataryl coenzyme A (HMG-CoA) reductase inhibitors routinely in children with dyslipidemia. (1)

· Infectious

Families of children with nephrotic syndrome should be counseled regarding the signs and symptoms of infections such as cellulitis, peritonitis, and bacteremia. If there is suspicion of infection, a blood culture should be drawn prior to starting empiric antibiotic therapy. In the case of spontaneous bacterial peritonitis, peritoneal fluid should be collected if there is sufficient fluid to perform a para- centesis and sent for cell count, Gram stain, and culture. The antibiotic provided must be of broad enough coverage to include Pneumococcus and Gram-negative bacteria. A 3rd-generation cephalosporin is a common choice of IV antibiotic. (3,5)

- Thromboembolic

Children who present with the clinical signs of thromboembolism should be evaluated by appropriate imaging studies to confirm the presence of a clot. Studies to delineate a specific underlying hypercoagulable state are recommended. Anticoagulation therapy in children with thrombotic events appears to be effective— heparin, low-molecular-weight heparin, and warfarin are therapeutic options. (4,7)

- Obesity and Growth.

Glucocorticoids may increase the body mass index in children who are overweight when steroid therapy is initiated, and these children are more likely to remain overweight. Anticipatory dietary counseling is recommended. Growth may be affected in children who require long-term corticosteroid therapy. Steroid-sparing strategies may improve linear growth in children who require prolonged courses of steroids. (2)

- Eating, Diet, and Nutrition

Children who have nephrotic syndrome may need to make changes to their diet, such as limiting the amount of sodium, often from salt, they take in each day
reducing the amount of liquids they drink each day
eating a diet low in saturated fat and cholesterol to help control elevated cholesterol levels
Parents or caretakers should talk with the child's health care provider before making any changes to the child's diet.(2)

Aim of the study

To study the trigger factors of relapses in Childern with steroid sensitive nephrotic syndrome.

Patient and methods

A retrospective study in Al Immamain Al Kadimain Medical City from period 1/11/2018 to 20/1/2019
Study sample was 40child with steroid sensitive nephrotic syndrome collected from pediatric nephrology clinic. Data collected from files records of the patients and direct interview with parents and doctors caring of children.
Data include: Name,Age .Age of Diagnosis ,sex ,residency ,No. of relapses for the last 12 Months and cause of relapses .(appendix 1)

Definition used:

- Frequent relapse NS :steroid sensitive NS with 2 or more relapses within 6m or more than 3 in one year. (1)
- inFrequent relapse NS :steroid sensitive NS with less than2 relapses within 6m. (1)

exclusion criteria :

children with congenital nephrotic syndrome.
children with secondary nephrotic syndrome

Statistical anslysis :

the data were analyzed manually and represented in the form of frequency and percentage for certain variables in tables design using Microsoft excel software

Results

• Total no. Of patients in this study were 40 children who had 58 relapses (table1)
• No. Of males were 23 (57,5%) while no of females were 17(42,5%) with male;female ratio 1,35:1(table2)

• Regarding age of patients table 3 show 13patients between 1-5y (32,5%), 18 patients between 5-10y (45%)and 9 (22,5)patients above 10y

• Age range was from 1 year to 14 years

• While regarding the age of onset of NS , , 16 (40%)patients were between 1-5 y, 13 (32,5%)patients between 5-10y and 11 (27,5%) patients above 10y

• Distribution of patients according to the residency as show in table 4 was 24 patients (60%) were lived in urban areas while 16 patients (40%) were lived in rural areas

• The no of patients with frequent relapses were 23 (57,5%) while patients with infrequent relapses were 17(42,5%) table5

• Table 6 demonstrate that the trigger factors for relapses were 51 (88%) relapses caused by infections , 3 (5,2%)relapses caused by examinations, 2 (3,4%) relapses caused by change weather and also 2 caused by stop steroid

• From the infections causes the UTI was the commonest cause that induced relapses (31) (53,5%) , the next common cause was URTI that cause 15 relapses (25,9%) , while pneumonia cause 3 relapses (5,2%) and gastroenteritis cause 2 relapses (3,4%)

• Tablet 7 demonstrate relation between trigger factors and gender , the UTI was the component cause of relapses in females(17) 63%, while (14) 45,1%in males . On other hand URTI was the commonest cause of relapses in males (11) 35,4% compare to (4) 14,8% in females

Table 1 GENDER DISTURBUTION OF CHILDERN WITH NS

gender	No.	Percentage
male	23	57.5%
Female	17	42.5%
total	40	100%

Table 2 distribution of childern with NS according to age group

Age(yr)	NO.	PERCENTAGE
1-5yr	13	32.5%
5-10yr	18	45%
>10YR	9	22.5%
total	40	100%

Table 3 distribution of childern with NS according to the age of onset

Age(yr)	NO	PERCENTAGE
1-5yr	16	40%
5-10yr	13	32.50%
10yr	11	27.50%
total	40	100%

Table 4 DISTURBUTION OF PATIENT ACCORDING TO RSIDENCY

Residency	NO	percentage
Urban	24	60%
Rural	16	40%
Total	40	100%

Table 5 DISTIRBUTION OF PT ACCORDING TO FREQUENCY OF RELAPSES

Frequency	NO	PERCENTAGE
Frequent relapse	23	57.5%
Infrequent relapse	17	42.5%
total	40	100%

Table 6 triggers factors for relapses in childern with NS

Trigger factors		NO	PERCENTAGE
Infection	UTI	31	53.50%
	URTI	15	25.90%
	CELLULITIS	0	0%
	PNEUMONIA	3	5.20%
	GATROINTERITIS	2	3.40%
	PERITONITS	0	0%
OTHERS	CHANGE WETHER	2	3.40%
	EXAMINATION	3	5.20%
	FAMILY STRESS	0	0%
POOR COMPLAINCE FOR TREATMENT	DOSAGE REDUCE	0	0%
	STOP STEROID	2	3.40%
TOTAL		58	100%

table 7 relation ship between triggers factors of relapses in childern and gender

Triggers factor	gender				total
	MALE	%	FEMALE	%	
UTI	14	45.1%	17	63%	31
URTI	11	35.5%	4	15%	15
PENUMONIA	2	6.5%	1	3.7%	3
GASTROENTRITIS	1	3.2%	1	3.7%	3
CHANFE WEATHER	1	3.2%	1	3.7%	2
EAMINATION	1	3.2%	2	7.4%	3
STOP STEROID	1	3.2%	1	3.7%	1
TOTAL	31	100%	27	100%	58

Discussion

• in medical references and books there is similar results of male predominance with m ; f ratio ranging from 4;1 to 1,3; 1 (nelson text book of Pediatric mention that ratio is 2;1) , (Takahashi , et al . Mention that the ratio 3:1) (1,12)

• The age of presentation in this study is similar to other reports (moorani ,2012 ,) (Nelson text book mention that the the most prominent age of presenting between 5-9y
• Also the age of onset is similar to previous study (shatha et al 2016) (the prominent age of onset between 5-10y), (Sinha, et al , mention that the age range of onset of NS is 5-10yr) (9,10,11)

• Distribution of patients were mainly from urban areas , and this is because the referral of patients from other areas to Al Imamman medical city because presence of a spicialized nephrology clinic .

• This Study show frequent relapses were more than infrequent , this similar to other study's (sarker et al., study show the frequent relapses 68% while infrequent constitutes the other prcentage) , (Rahi et al ,. Mention that the frequent relapses is more than infrequent in 71,3%) ; (shatha et al ,. Mention that the percent of frequent relapses was 77,5%) (10,14,15)

• Regarding the trigger factors of relapses , they were more predominant with infection and this is similar to other study (moorani mention that infection constitute 79% of all causes of relapses) (shatha et al,. Also mention that the infections was the commonest cause of relapses in 63,59%of all the relapses) while other causes have little effect in compare with infections (9,10)

• This study show the causes of relapses in female were mainly caused by UTI and the results from this study came in agreement with (moorani et al , that mention the most common cause of relapses in females were UTI that account 34 relapses of 70 caused by infection) (Rahi et al ,. Also mention that the most common cause of relapses in females was RTI in 65,3% of all relapses in females) and this is because the female have many precipitating factors for UTI as e.g (short urethra , proximity of the urethral meatus to vagina). (9,14)

While the most common cause of relapses in male were URTI because of collection of patient during the winter season were URTI more common and total numbers of males in the study more than females and this agree other results (sarker et al ,. Mention that the common cause of relapses in male were URTI in near with UTI), (lombed, et al . Mention that the URTI is the most common cause of relapses in males in 28 of 50 relapses caused by infections)(13,15)

Conclusion

* males with (NS) more than females
* Most common age of presentation and onset of (NS) is 5-10yr
* Most common patients from urban areas
* Frequent relapses more than infrequent
* Most common cause of relapses was infections followed by examinations
* UTI was the commonest cause of relapses in infections causes followed by URTI
* There is a correlation between UTI and relapses in females and URTI and relapses in males

Recommendation

* Proper follow up of patients with NS
* Early detection of relapses and proper management
* Good search for sources of infections with relapses is indicated for treatment particularly UTI and URTI

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