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RESEARCH ARTICLE

NEPHROTIC SYNDROME AS INITIAL EPISODE AND RELAPSE IN IRAQI CHILDREN.

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Key words:-
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Abstract

Background: Nephrotic syndrome is a clinical syndrome defined by massive proteinuria responsible for hypo-albuminemia, with resulting hyperlipidemia, edema, and various complications.
Aim of the study: to see the clinical presentation of cases of nephrotic syndrome in IRAQI patients and the possible causes of relapses
Material and Methods: Forty children with nephrotic syndrome admitted to Al-Mansour Teaching Hospital. A full physical examination was done to each patient and all undergo the following investigations: Urinalysis, urine culture, serum cholesterol, total serum protein, serum protein electrophoresis and chest roentgenogram. Renal biopsy was done only for one patient. The treatment received and the outcome of these cases were recorded.
Results: The symptoms of associated infections (fever, cough, abdominal pain, vomiting and diarrhea) were more frequent among the patients with relapse than the newly diagnosed patients. The most obvious sign in all nephrotic patients was edema. Ascites found in (55.5%) of newly diagnosed cases , and in (31.8 %) of patients with relapses , Hypertension (blood pressure more than 95 % for age and sex) .(55.5 %) of patients with relapse who had hypertension , were frequent relapses. Abdominal tenderness was more common among the patients with relapse.
Discussion: The peak age incidence in this study was between 1-5 years and there was decreases in incidence below on and above 10 years of age. Edema was found as a symptom and sign. Localized edema in the periorbital area or in the legs at presentation was found only in small number of the patients (15%) this may be due to the delay in the consultation until the edema becomes generalized (table 4 and 5). Generalized edema was the most common presenting symptom in nephrotic patients and oliguria was the next common symptom.
Conclusion: Generalized edema was the most common presenting symptom in nephrotic patients and oliguria was the next common symptom.

Introduction:-

Nephrotic syndrome (NS) is a clinical syndrome defined by massive proteinuria responsible for hypo-albuminemia (serum albumin less than 2.5gm/dL), with resulting hyperlipidemia (serum cholesterol more than 200mg/dL),

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edema, and various complications especially hypovolemia, infection and thrombosis [1] [2]. It is caused by increased permeability through the damaged basement membrane in the renal glomerulus [3]. The pathophysiology of nephrotic syndrome: The glomerular capillaries are lined by a fenestrated endothelium that sits on the glomerular basement membrane, which in turn is covered by glomerular epithelium, or podocytes, which envelops the capillaries with cellular extensions called foot processes [4]. These processes interdigitate with special cell-cell junctions called the slit diaphragm which together forms the glomerular filter. Normally, larger proteins (greater than 69 kD) are excluded from filtration. Destruction of podocytes above a critical mass also leads to irreversible glomerular damage [5] [6]. Ninety percent of NS is idiuch idiopathic. Secondary cases such as Systemic Lupus Erythematosus (SLE) or Henoch Scholein Purpura (HSP) should be considered if there are atypical features [7]. Remission: Urine albumin nil or trace (or proteinuria less than 4 mg/m/h) for 3 consecutive early morning specimens. Relapse: Urine albumin 3+ or 4+ (or proteinuria more than 40 mg/m/h) for 3 consecutive early morning specimens having been in remission previously [2].

Prednisolone should be restarted once a relapse has been diagnosed: 2 mg/kg daily (maximum 60 mg) until the urine is negative or trace for three days, then 40 mg/m 2 /on alternate days for 4 weeks then stop or taper the dose over 4 to 8 weeks [8] [9]. Frequent relapses: Two or more relapses in the initial six months or more than three relapses in any twelve months. Steroid dependence: Two consecutive relapses when on alternate day steroid or within 14 days of its discontinuation [2]. While most of the children with primary NS respond to steroid treatment, 10 to 20 % of the patients are steroid resistant [10].

Many of these children may require vitamin D or calcium supplements to prevent bone loss. The nurse should also educate the family on how to measure urine output on a daily basis and record the amount-this will provide an indication of how the disease is progressing [11]. Finally, a dietary consult should be obtained to educate the patient on a low-salt diet to prevent an aggravation of the edema [12]. The long-term risk of renal failure in these patients is low. Patients who show a poor response to steroids usually have a poor outcome. For those who develop nephrotic syndrome (NS) due to a secondary cause, the morbidity is primarily related to the cause. Diabetic patients who respond to ACE inhibitors may develop slowing down of proteinuria and stabilize renal function. Those who develop amyloidosis usually have a guarded prognosis [13] [14] [15].

Aim of the study:
to see the clinical presentation of nephrotic syndrome in IRAQI children in the initial episode and the relapse

Material and Methods:-

Forty children with nephrotic syndrome admitted to Al-Mansour Teaching Hospital between November 1996 and May 1997 were all included in this study. The patients were categorized into:
Newly diagnosed cases which include

1. Cases considered as initial episode of NS (other than congenital or secondary cases).
2. Cases considered as congenital NS when the age of the onset was below one year
3. Cases considered as secondary NS when associated with primary diseases.

Previously diagnosed cases of NS presented with relapses.

These cases were studied with emphasis on the symptoms and signs of presentation, age of onset, previous relapses and family history.

A full physical examination was done to each patient and all undergo the following investigations:
Urinalysis, urine culture, serum cholesterol, total serum protein, serum protein electrophoresis and chest roentgenogram. Renal biopsy was done only for one patient. The treatment received and the outcome of these cases were recorded.

Results:-

The total number of patients studied was forty. Fourteen (35 %) patients were cases with initial episode of NS 2 (5%) patients were congenital nephrotic syndrome, and 2 (5%) patients were secondary nephrotic syndrome (one of them is a case of SLE and other one is a case of henoch-schonlein purpura). Twenty two (55 %) patients were known cases of nephrotic syndrome presented with relapses (Table 1).The age incidence of the patients ranged

between 2 months and 12 years with peak age incidence between 1-5 years (75%). Male to female ratio was 1.3: 1 (table 2). Family history of nephrotic syndrome was found in 20 % of all the patients with NS (Table 3).The most frequent symptom of NS was edema which is found in all the patients, either as generalized or localized edema.

Oliguria was the next frequent symptom.

The symptoms of associated infections (fever, cough, abdominal pain, vomiting and diarrhea) were more frequent among the patients with relapse than the newly diagnosed patients (Table 4) .The most obvious sign in all nephrotic patients was edema. Ascites found in (55.5%) of newly diagnosed cases , and in (31.8 %) of patients with relapses , Hypertension (blood pressure more than 95 % for age and sex) was more frequent among the patients with relapses mainly those who are frequent relapses (Table 10). Abdominal tenderness was more common among the patients with relapse (Table 5).

Two groups of relapses were found:

1. Infrequent relapses; 14 (63.6 %) patients who had 3 relapses or less per year. Frequent relapsers; 8 (36.4 %) who had more than 3 relapses per year or relapse twice per 6 months (Table 6).
2. All patients who presented with relapse showed clinical, laboratory or radiological evidence of infection.
3. Evidence of peritonitis (anorexia, repeated vomiting, abdominal pain and generalized abdominal tenderness was found in (31.8 %) of relapses, pneumonia in the chest roentgenogram was found in (36.4 %) of relapsers, growth of bacteria in urine culture was found in (31.8 %) of relapsers (Table 7).
4. Serum albumin less than 2 g/dL was found in (77.7 %) of newly diagnosed cases and in (95.4 %) of patients with relapses as shown in table 4. Serum cholesterol more than 250 mg/dL was found in (50 %) of newly diagnosed cases, and (72.7 %) of patients with relapses (table 8).

Patients who had low serum albumin and high serum cholesterol at the sometime were (60 %) of all our patients as shown in table 8.Follow up of the patients showed: Six patients (3 with initial episode , one CNS, one secondary NS and one with a relapse) left the hospital with proteinuria. Eleven (78.5 %) patients with initial episode of NS showed remission within 5-14 days. One patient of CNS died because of septicemia. One patient of secondary NS (Henoch - Schonlein nephritis) showed steroid resistance. Seventeen (77.2 %) patients with relapse showed remission within 5-14 days. One (4.6 %) patient with relapse showed steroid dependency. Two (9 %) patients with relapse showed steroid resistance (one of them respond to cyclophosphamide course of 12 weeks with alternate day prednisolone without renal biopsy , the other one showed memberano-proliferative glomerulonephritis by renal biopsy and passed to renal failure). One (4.6 %) patient with relapse died because of cerebral thrombosis.

Table 1:-Nephrotic patients included in the study

patients		
	N	%
Initial episode	14	35
Congenital	2	5
Secondary	2	5
Relapse	22	55
Total	40	100

Table 2:-Age of onset and gender distribution of nephrotic syndrome

Age of onset	Male	Female	Total	Total
			N	%
< 1 year	1	1	2	5
1-5 year	18	12	30	75
> 5-10 year	3	4	7	17.5
>10 year	1	0	1	2.5
Total	23	17	40	100

Peak age incidence 1-5 year
Male to female ratio = 1.3: 1

Table 3:-Familial incidence in nephrotic syndrome

Patients	Total N	Family history of NS	
		N	%
Initial episode	14	2	14.2
Congenital	2	1	50
Secondary	2	0	0
Relapse	22	5	22.7
Total	40	8	20

Table 4:-Frequency of symptoms in nephrotic syndrome

Symptoms	Newly diagnosed		Relapse		Total	
	N	%	N	%	N	%
Edema	18	100	22	100	40	100
(generalized)	16	88.8	18	81.8	34	85
(localizcd)	2	11.2	4	18.2	6	15
Oliguria	14	77.7	19	86.3	33	82.5
Anorexia	12	66.6	14	63.6	26	65
Cough	10	55.5	14	63.6	24	60
Fever	8	44.4	12	54.5	20	50
Vomiting	6	33.3	9	40.9	15	37.5
Abdominal	4	22.2	16	72.7	20	50
Dysuria	3	16.6	2	9	5	12.5
Gross hematuria	3	16.6	0	0	3	7.5
Diarrhea	1	5.5	8	36.3	9	22.5

Table 5:-Frequency of signs in nephrotic syndrome

signs	Newly diagnosed		Relapse	
	N	%	N	%
Periorbital edema	18	100	22	100
Leg edema	17	94.4	20	90.9
Ascitis	10	55.5	7	31.8
Hypertension	5	27.7	9	40.9
Abdminal tenderness	3	16.6	9	40.9
Genital edema	3	16.6	6	27.2
Hepatomegally	3	16.6	6	27.2
Dyspnea	1	5.5	3	13.6

Table 6:-Frequency of relapse in nephrotic patients

Relapsers		
	N	%
Infrequent relapsers	14	63.6
Frequent relapsers	8	36.4
Total	22	100

Table 7:-Infections that associated with the relapse in nephrotic syndrome

Infections		
	N	%
Pneumonia in the CXR	8	36.4
Evidence of peritonitis	7	31.8
Positive urine culture	7	31.8
Total	22	100

Table 8:-Serum albumin and serum cholesterol in patients with nephrotic syndrome

Patients	Total	S.albumin <2.5g/dL		S.cholesterol <200mg/dL		Both S.cholesterol > 200 mg/dL S.albumin<2.5g/dL	
	N	N	%	N	%	N	%
Newly diagnosed	18	14	77.7	9	50	8	44.4
Relapse	22	21	95.4	16	72.7	16	72.7
Total	40	35	87.5	25	62.5	24	60

Table 9:-Outcome of nephrotic patients in the study

Outcome	Newly diagnosed Initial episode		Congenital		Secondary		Relapse		Total	
	N	%	N	%	N	%	N	%	N	%
Left the hospital With proteinuria	3	21.5	1	50	1	50	1	4.6	6	15
Remission within 5-14 days	11	78.5	0	0	0	0	17	77.2	28	70
Steroid dependency	0	0	0	0	0	0	1	4.6	1	2.5
Steroid resistance	0	0	0	0	1	50	2	9	3	7.5
Death	0	0	1	50	0	0	1	4.6	2	5
Total	14	100	2	100	2	100	22	100	40	100

Table 10:-Nephrotic patients with hypertension

Nephrotic patients	**Total number**	**Hypertensive**	
		N	**%**
Initial episode	14	1	7
Infrequent relapsers	14	4	28.5
Frequent relapsers	8	5	62.5

Discussion:-

The majority of patients included in this study showed typical presentation of Idiopathic Nephrotic Syndrome (INS) either as an initial episode or as a relapse, however couldn't categorized them as INS without full investigations.

Those patients with typical presentation accounted to 90% of all the patients (Table 1). This finding agreed with done by (Hill AJ, *et. al.* 2016) [16]. Also table one showed that only two cases were of congenital type, this is because CNS is a rare condition with poor prognosis [10].

As shown in this study only one patient had persistent protein-urea and other died because of septicemia. The peak age incidence in this study was between 1-5 years and there was decrease in incidence below one and above 10 years of age (table 2).

Edema was found as a symptom and sign. Localized edema in the periorbital area or in the legs at presentation was found only in small number of the patients (15%) this may be due to the delay in the consultation until the edema becomes generalized (table 4 and 5). Generalized edema was the most common presenting symptom in nephrotic patients and oliguria was the next common symptom.

Cough, fever, vomiting, abdominal pain and diarrhea were more frequent among patients with relapses than those with initial episodes , as relapses often associated with an acute intercurrent illness and there is an increased susceptibility to bacterial infection during relapse. Patients with relapses, especially frequent relapses have higher risk of developing serious infections, and prolonged steroid therapy significantly contributes to this [17].

All our patients with relapses had infections either peritonitis or pneumonia or UTI (Table 8). During acute infection many children with NS will have transient proteinuria that resolves spontaneously. So it is important to rule out such infections before initiating therapy. If we exclude congenital and secondary NS, only one (7%) patient had hypertension in the initial episode, while 40.9% of relapse cases had hypertension. 62.5% of frequent relapsers had hypertension. This indicate serious problem of frequent relapses from the side effects of multiple courses of daily steroid and prolonged maintenance therapy

In this study the number of relapsers who had low serum albumin (less than 2.5g /dl) or high serum cholesterol (more than 200 mg / dl) was more than the number of patients with initial episode NS who had similar biochemical values (Table 8) . Although the nephrotic patient is not described as steroid resistant until 4 weeks of treatment have been completed, most our patients (70%) achieved remission within 5-14 days. Steroid resistant NS may respond to an extended course (3-6 months) of cyclophosphamide, pulse methyl prednisolone or cyclosporine. In this study one patient steroid resistant showed remission after a course of cyclophosphamide (2 mg / kg / day for 12 weeks) in combination with alternate day prednisolone.

Conclusion & Recommendation:-

1. Generalized edema was the most common presenting symptom in nephrotic IRAQI children and the oliguria was the next common symptom.
2. Nephrotic patients presented with relapses often have infections at presentation and the most common infections in nephrotic patients are pneumonia, peritonitis and urinary tract infection, so a high index of suspicion and prompt evaluation (including blood culture, urine culture and peritoneal fluid culture) with early starting of antimicrobial agents, is recommended. A delay in starting steroid therapy 7-10 days until controlling infections in the relapses is recommended to reduce steroid toxicity and to give the patient a chance for spontaneous remission which could not be achieved in our series because of different opinions about relapse.
3. Nephrotic patients with relapses had lower serum albumin and higher serum cholesterol, when compared with initial episodes.
4. Most children with idiopathic nephrotic syndrome as initial episodes or relapses respond to steroid within the first 2 weeks of treatment.
5. Hypertension is more common among frequent relapsers nephrotic patients than those who are infrequent relapsers, this may be due to steroid toxicity or due to pathology other than MCNS, so renal biopsy is a useful aid for diagnosis of atypical nephrotic syndrome and it is recommended as indicated.
6. Cyclophosphamide is a useful therapy in the treatment of steroid resistant nephrotic syndrome.

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