EPIDEMIOLOGY AND CLINICOPATHOLOGIC CHARACTERISTICS OF CHILDHOOD NEPHROTIC SYNDROME IN LIBYA SINGLE CENTER EXPERIENCE

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ABSTRACT

Idiopathic, non-congenital Nephrotic syndrome (NS) of childhood is characterized by massive proteinuria and hypoalbuminemia, leading to oedema and hypercholesterolemia. Other clinical findings, such as haematuria and hypertension, are observed in a small fraction of patients. To identify the exact pattern of NS in Libyan children, incidence of disease, and out-comes of NS. This study was retrospectively carried out on 329 children (227 male and102 female), male: female was 2.2:1, aged (mean=4.9 ±3.2 year) at the onset of the disease. All patients with Idiopathic Nephrotic Syndrome. This diagnosis was made according to the criteria of the international study of kidney disease in children (ISKD). An average admission at Nephrology ward was 214 cases/ year; correspond to 5% of total hospital admission. 30.3 % were newly diagnosed Nephrotic Syndrome (65 newly diagnosed nephrotic patients/ year). Sixty nine % of children were with good sensitivity to steroid, 24.3% with steroid dependent and 6.7% were steroid resistant. Viral screen was done in 226 patients 68% ,28 children were positive for HCVAb by ELISA 8.5% of total cases,HBSAg was positive in one female ,no one with HIV. HCVAb positive cases 78.57% of them were steroid dependent & steroid resistant with frequent admission. The out-comes were as follow; 18 patients got hypertension, one patient with DM, two patients with hypothyroidism, one patient with cataract and glaucoma , 8 patients were died and 135(41.3%) got complete remission. with regular treatment and follow up, the prognosis of idiopathic Nephrotic syndrome is good,with better organized schedules of management, has substantially reduced the Mortality of SRNS (steroid responder Nephrotic syndrome), but death still occurs, primarily from hypovolemia, Thrombosis and sepsis. Relapses eventually cease. Blood pressure and renal function remain Normal.

KEY WORDS: Nephrotic Syndrome, Response to treatment, Outcome.

INTRODUCTION

Nephrotic syndrome is a clinical state characterized by heavy proteinuria (>40 mg / m2 / hour), hypoalbuminemia, edema and hyperlipidemia[(1)]. It is a disorder of glomerular permeability that may be primary or secondary to an overt systemic disease[(2)]. Research on pathogenesis has emphasized the importance of T lymphocyte dysregulation and vascular permeability factors that might alter podocyte function and permeability[(3)]. While mutation in genes that encode important podocyte proteins have also been identified, a hypothesis unifying available evidence on pathogenesis is yet to be proposed. The tendency of Nephrotic syndrome to manifest and relapse after viral infection or atopic episode, the association with HLA antigens and Hodgkin's lymphoma, and the therapeutic response to steroids and Cyclosporine (CsA) and The occurrence of prolonged remissions following measles, which down regulates CMI (cell mediated immunity) support this view[(3)]. Nephrotic syndrome is a common renal disorder with incidence of 20-40/million population /year in western countries[(4)], there are no published reports from Libyan children. Minimal change Nephrotic syndrome (MCNS) is the most common cause of idiopathic Nephrotic syndrome in children. However, most studies from different countries have reported an increasing incidence of focal segmental glomerulosclerosis (FSGS) in childhood[(5)]. Patient with primary Nephrotic syndrome may be divided into two groups depending upon the response to steroids. Steroid sensitive are those who achieve remission during first 28 days of prednisone therapy. Steroid Resistant are the patients who have not entered into remission by the end of 28 days of steroids therapy in a dose of 60mg / m2 / day followed by three pulse of methyl prednisolone (30 mg / kg / dose) maximum dose is 1gm over a period of one week[(6)]. Patients with Nephrotic syndrome are at risk for life threatens Infections and thromboembolic episodes. Long-term effects of persistent hyperlipidemia and prolonged steroid therapy are increasingly recognized. Remission of proteinuria follows; corticosteroid therapy has greater prognostic value, in relation to long-term outcome, than the precise renal histology. Prospective studies show that prolonged duration of therapy for the initial episode results in sustained remission and reduced frequency of relapses[(3)]. The management of steroid-resistant Nephrotic syndrome is difficult; most patients failing to achieve remission show progressive renal damage. Calcineurin inhibitors (Cyclosporine, tacrolimus) are capable of inducing remission in a significant proportion of patients, but at risk of nephrotoxicity. Reduction of proteinuria is also possible; in children, using angiotensin converting enzyme inhibitors and/ or angiotensin receptor blockers[(3)].

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PATIENTS AND METHODS

A retrospective study was performed on 329 children with Nephrotic syndrome, the children were identified from nephrology clinic records over a 10 year period (January 1995-December.05), in Tripoli children′s hospital.

This diagnosis was made according to the criteria of the international study of kidney disease in children (ISKD)[7]. Only patients who were on regular follow up selected, patients who were on irregular follow up excluded.

1- We recorded the age of patients at first attack of the disease, features at presentation as hematuria or hypertension, renal impairment, hypo-complementaemia. ↓C3 level and the response to steroid treatment.
2- Family history of as {(renal stone, UTI, RF and others excluding NS), nephrotic syndrome, and Atopy}, if patients is asthmatic.
3- Laboratory investigations including :
-Estimation of the amount of protein in 24 hours urine collection (gm/24hrs), serum albumin. Total protein in the blood, Serum cholesterol, blood urea level and serum creatinine level., Viral screen; as HCVAb, HBSAg & HIV.

All patients after presentation were seen at least monthly, and weekly in cases who received cyclophosphamide. At each clinic visit, patients had their height and weight recorded. Clinic review included recording of any relapses of NS, steroid regimen used, days to achieve remission and weaning regimen of steroid therapy. Blood pressure was recorded using an appropriately sized cuff and a mercury sphygmomanometer, signs of infection or complication, Qualitative urinalysis was performed for evidence of proteinuria and CYA blood levels were carried out every three months.

RESULTS

Total admission at Nephrology word in four years from (Juan 01 – Dec 04) was 857 cases, with an average of 214 cases/ year, Out of these cases, 260 patients were newly diagnosed Nephrotic Syndrome children by average of 65 patients/ year; correspond to 30.3 % of nephrology admission. . Annual incidence was 2.7/ 100.000/ year. Total out patients department (O.P.D) cases at nephrology clinic are 2974 patients. 24.2% of them were Nephrotic patients.

Retrospectively we studied 329 children with idiopathic Nephrotic syndrome, all had been regularly followed at nephrology clinic in children hospital in Tripoli Libya (January 1995 – December.05), [227 (69%) males and 102 (31%) females], with mean age 4.9 ± 3.2 years at presentation (table 1).

(Table 1) Baseline Characteristics of Nephrotic Syndrome children

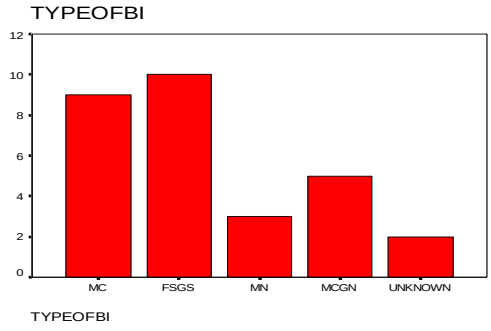
	Mean		St D
Age (Year)	4.9		±3.2
	Atypical age < 2 & >10	18.8%.	
	2 - 10	81%	
Sex	Males	227 (69%)	
	Females	102 (31%)	
S.Albumin (gm/dl)	1.77	±0.5	
S. Cholesterol (mg/dl)	356	±119.68	
24 Hrs Of Urinary Protein (gm)	3.9	±2.9	
Average day of treatment after which patient got Response (Days)	11	±6.6	
T.Protein (gm/dl)	4.23	±0.8	
Steroid Response	Good Response	69%	
	St. Dependent	24.3%	
	St. Resistant	6.7%	

A majority of our patients were from Tripoli (130 patients 39.4%) (table 2).

(Table 2) Referred Areas of Nephrotic Syndrome

	frequency	percentage
Tripoli	130	39.4%
West of Tripoli	92	27.9%
East of Tripoli	58	17.6%
South of Tripoli	13	3.9%
missing	36	11.2%
total	329	100%

Renal biopsy was done to 28 cases, who were presented with atypical features as (age at presentation less than 2 years or more than 10 years, persistent haematuria, renal impairment, hypocomletenemia), SR, SD, or had a complication of steroid therapy, 9 children had MCD (32.1%), 10 with FSGS (35.7%) , 3 had MN (10.9%) , 4 had MCGN (14.3%) and 2 with unknown result (7.1%). The result of the biopsy did not have an influence on the current data analysis (figure 1).



(Figure 1) Types of Renal Biopsy

A typical presentation showed in (table 3), 62 patients 18.8% presented with high blood pressure, 53 patients 16.1% presented with microscopic haematu-

ria, 40 patients 12.1% with macroscopic haematuria, high urea in 13 patients 3.9%, low complement (C3) in 10 patients 3.3%, and 5 patients presented with high creatinin (1.5).

(Table 3) Atypical presentation of nephrotic children.

	frequency	percentage
↑ BP	62	18.8
Hematuria microscopic macroscopic	93 53 40	28.2 16.1 12.1
↑ creatinine	5	1.5
↑ urea	27	8.2
↓ complement C3	10	3.1

Chemotherapy was given to 62 patients; Cyclophosphamide was given to twenty five children (43.1%).Cyclosporine A was given to twelve children (20.7%), cyclosporine has been shown to be effective in inducing or maintaining remission in frequently relapsing steroid-dependent Nephrotic syndrome. Levamisole was given to seven patients (12.1%). Mycophenolate mofetile (cellcept) MMF was given to two patients with steroid resistant NS renal biopsies were FSGS both had no response. Mendoza protocol (pulse Methyl Prednisolone, prednisolone and cyclophosphamide) was given to four resistant focal segmental glomereulosclerosis Nephrotic children, all got remission, with no side effects.

33.9% of patients got relapses in winter, 29.1% in summer, 22.9% in spring and lastly 14.1% in autumn (table 4), increased incidence of relapses in cold months and after respiratory infection points on the possible role of some viruses in etiopathogenesis in some NS patients.

(Table 4) Seasonal variation of nephrotic syndrome.

	frequency	percentage
winter	113	34.4%
summer	95	28.8%
spring	75	22.8%
autumn	46	14%.

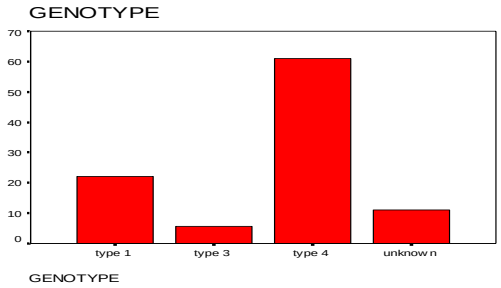
There is a greater incidence of a topic diseases particularly asthma, eczema and hay fever in children with steroid responsive Nephrotic syndrome and occasionally there is a clear-cut association of relapse of NS with allergic events.

These have been noticed in our patients; forty two cases 17.9% had bronchial asthma, and seventeen patients (5.2%), out of 230 patients had positive family history of atopy, eighteen children (5.5%) had positive family history of renal diseases as CRF, UTI and Renal stone. Twenty four patients (7.3%) had positive family history of Nephrotic syndrome.

Viral screen was done in 226 patients (68.7%), and was not done in 103 patients (31.3%) twenty eight cases (8.5%) of total had positive HCVAb and negative in 198 children. HBSAg was positive in one case, HIV did not seen in any one.

In the present work, 28 patients showed HCVAb positive by ELISA; further investigated using a PCR technique, when only 18 patients were positive for HCV-RNA in their sera; while seven patients were negative; three patients PCR did not done.

Genotypes were type 1 in four cases; type 3 in one case; type 4 in eleven cases and two cases with unknown results (figure 2).



(Figure 2) Genotypes of positive HCVAb patients

Complication of NS (table 5) in general in this study were as follow thirteen patients developed hypertension, (3.9%) two children with diabetes mellitus (DM), (0 .6%), hypoth yroidism was seen in two patients (0.6%), severe infections was seen in six patients (1.8%), thrombosis in one child (0.3%), three patients (0.9%) got renal failure, one patient had hypertension & infection, four got hypertension & renal failure (1.2%), eight patients died (2.4%), 32 patents loss follow up (9.7%).

(Table 5) complications Of Nephrotic Syndrome.

	frequency	percent
hypertension	13	3.9
DM	2	0.6
hypothyroidism	2	0.6
infection	6	1.8
thrombosis	1	0.3
RF	3	0.9
↑ BP & infection	1	0.3
BP & RF↑	4	1.2
Others(cataract and glaucoma)	3	0.9
transplant	1	0.3
died	8	2.4

The long-term remission of our cases (table 6), 135 children got complete remission and stop steroid therapy. 40 were females, 95 were males, and F:M is (2.4:1). Mean age is 9.3 years in male and 9.2 years in females. Mean duration of follow up until got remission was 3.6 years. 1-2 years off treatment, total number was 22 patients, 2-4 years duration of off therapy we had 65 patients, 5-7 years off therapy were 33 patients, 8-10 years off treatment there were 13 children, 2 boys had more than 10 years off therapy.

(Table 6) Long-Term Remission.

Duration Of Remission (In Yrs.)	Number Of Patients Total (135 41.3%)	Male Mean Age (9.3 Yrs.)	Female Mean Age (9.2 Yrs.)
1 – 2	22	17	5
2 - 4	65	46	19
5 - 7	33	23	10
8 - 10	13	7	6
> 10	2	2	0

DISCUSSION

The exact pattern of Nephrotic syndrome in Libya is not well known; this study reviewed the mode of presentation of Nephrotic syndrome in Libyan children. Long-term outcome attempts to find treatments that could induce a remission and thus prevent the progression of the disease to end stage renal failure, with good outcome. Nephrotic Syndrome is a common renal disorder. More than half of the children diagnosed with Nephrotic Syndrome will have relapses. These can be infrequent relapses [IR; < 2 in 6 months or < 3 in a year] or frequent relapses [FR; > 2 in 6 months or > 3 in a year]. Patients who relapse while on alternate day steroids or within one month of discontinuation of steroid therapy are considered steroid-dependant (SD) (J pediatric, 1982, 101; 514-18).Patients with an IR course have a better long-term prognosis and many of them have minimal change disease without mesangial hypercellularity or sclerosis. There were 69% of patients with IR (good Response), 24.3% with FR (steroid dependant) and 6.7% (18 cases) ,are Resistant to steroid, Some cases become late non responder and at the end of our study the percentage of steroid Resistance increased to 17.3%, and eleven patients were in the beginning steroid resistant later on responded on alternate day therapy, data from the Literature indicate that 40 % of relapses are represented by FR and SD patients[11, 12]. It is possible that our patient population will have a different steroid–response distribution in the subsequent years. Sixty-two patients received chemotherapy in addition to steroid therapy. Of our patients 25 children (43.1%) was treated with Cyclophosphamide by dose of 2.5 mg/kg/day in a single daily dose for 12 weeks with alternate day prednisolone therapy, to induce long- term remission & to prevent Bone Marrow suppression, complete blood count was done weekly, we omit the dose when WBC count decreased to less than 3.5×10^3 /mm^3. We find 70.8% of patients remained in remission, 25% of these patients got relapse after one year, and subsequent relapses are glucocorticoid sensitive. There was no complication, except transient leucopenia. Only one case developed haematuria. These in compare to other study, the response to Cyclophosphamide is also related to the responsiveness to steroids. Seventy percent of children with frequent relapses remained in remission after an eight-week course of Cyclophosphamide, whereas only 30% of steroid-dependent patients had prolonged remission[11]. Twelve children (20.7%) received Cyclosporine A for 18 months, 33% got relapse after stopping Cyclosporine A therapy, and 16.7% got relapse in a second year. Reversible gum hyperplasia and hypertricosis noticed in one patient, with no one with renal failure. CYA has been shown to be effective in inducing or maintaining remission in patients with frequently relapsing or steroid – dependent Nephrotic Syndrome[13-15]. In one report, 13 of 47 children with refractory Nephrotic syndrome who received CYA at a dose of 6mg/kg/day failed to respond[16]. These patients had higher plasma cholesterol concentrations than the responders and sub therapeutic whole blood through CYA levels (71 ng / ml versus 162 ng / ml in responders). Seven of the non-responders were given higher CYA doses of 10 to 14 mg/kg/day; five responded without evidence of nephrotoxicity. Unfortunately, CYA induced remission is not long – lasting and most patients relapse within the few months following cessation of treatment. Therefore, CYA may have to be administered for long periods, exposing to the risks of nephrotoxicity. Levamisole was given to 7 patients (12.1%) by a dose of 2.5 mg/Kg on alternate day for one year and we noted that all patients got relapses while they were on treatment or soon after cessation of treatment especially after stopping prednisolone, Levamisole, which stimulates the immune system, has been shown to have a steroid-sparing effect in these settings[17,18]. The British Association for pediatric Nephrology performed a multicenter study in which 61 children received either Levamisole (2.5mg/Kg) on alternate day to maximum dose of 150 mg or placebo[19]. Fourteen patients in the Levamisole group and four in the control group were still in remission after 112 days despite prednisone withdrawal. However, most patients relapsed within three months after cessation of treatment. Azathioprine given to 2 patients with incomplete data, MMF also, given to 2 patients (3.4%) with no response (renal biopsies in both of them showed FSGS) one presented with Renal Failure , renal Transplant was done from un related donor on Augaust.03. Tune-Mendoza protocol (pulse Methyl Prednisolone Therapy), was given to four patients with steroid resistant NS and renal biopsies were FSGS (6.9%). All got remission with no side effects. Pulse Methyl Prednisolone is given by a dose of 30mg/Kg intravenously, oral prednisolone (2mg/Kg every other day), and Cyclophosphamide[20, 21]. At an average of over six years of follow up, 21 of 32 children were in complete remission and the five-year incidence of end stage renal disease was approximately five percent versus 40 percent in historical controls[21]. Twenty two patients went to long-term remission on slow tapering of prednisolone over long time. The presence of Haematuria both gross and microscopic did not correlate with the Steroid Sensitivity. The presence of hypertension at presentation did not correlate with the Steroid Sensitivity. Observed increased incidence of relapses in cold months and after respiratory infection points on the possible role of some viruses in etiopathogenesis in some NS patients[22]. There is a greater incidence of a topic disease, particularly asthma, eczema, hay fever, in children with steroid Responsive NS than in matched controls, and occasionally there is a clear-cut association of relapse of NS with allergic events[1]. Viral screen was started as routine investigation in 2002, 28 cases (8.5%) of total had positive HCVAb & HBSAg was

positive in one case, HIV did not seen in any one. Hepatitis C Virus has been identified as the major cause of transfusion associated hepatitis[23]. In addition HCV infection is now recognized as a major cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma[24] although the introduction of ELISA into routine practice as a diagnostic test for HCV infection, non- specificity has been a significant problem. Nowadays, detection of the HCV-RNA genome in serum is based on a PCR technique; which is the most specific marker for HCV infection in either symptomatic or a symptomatic patients and can provide direct evidence for active viremia[25] .In the present work, 28 patients showed HCVAb positive by ELISA; further investigated using a PCR technique, when only 18 patients were positive for HCV-RNA in their sera; while 7 patients were negative; 3 patients PCR did not done.

Several explanations were suggested for the negativity of HCV-RNA by PCR in sera of ELISA positive patients.

Firstly; HCV is typical of RNA viruses in having a high mutation rate particularly in the envelope region with average 10-13 to 10-14 base substitution/ genome/ year[24].

Secondly HCV is present in very small amount in blood that may be below detection limit by PCR[26,27].

Thirdly**,** the existence of various HCV genotypes and their variable distributions, hence the success of PCR amplification depends on the selection of the primer set[28].

Finally, infected subjects may have cleared the HCV while remaining anti-HCV positive[24].

CONCLUSION

The widespread use of antibiotics and glucocorticoids, together with better organized schedules of management, has substantially reduced the Mortality of SRNS (steroid responder nephrotic syndrome), but death still occurs, primarily from hypovolemia, Thrombosis and sepsis. Relapses eventually cease. Blood pressure and renal function remain Normal.

If end-stage renal failure does develop in MCNS patients, it is a most unusual event and reports of its occurrence must be scrutinized very carefully to assess the adequacy of the initial histological examination or the possibility of the superimposition of another glomerular disease.

RECOMMENDATIONS

- Steroid should be given in the first attack by dose of 2 mg / Kg / day for four Weeks, and then if there is response we shift to alternate day therapy by the same dose for eight weeks, the slow tapering to be to decrease the evidence of relapse in the first year.
- cyclophosphamide therapy is better if given to steroid sensitive patients at Starting to remission and for 12 weeks, this duration give good result, less side effects and prolonged remission.
- Methyl prednisolone pulse therapy is recommended in steroid resistant patients especially FSGS TYPE.
- Cyclosporine A given to children who relapse after administration of an alkylating agents or who refuse to take the drug due to fear of side effects.
- Viral screen is recommend before starting any type of treatment and with every admission.

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