

ORIGINAL ARTICLE

OUTCOME OF CHILDHOOD ONSET FIRST EPISODE OF NEPHROTIC SYNDROME

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ABSTRACT

Background: Most patients with idiopathic nephrotic syndrome (NS) are steroid-responsive, about 50% relapse and often become steroid-dependent. The aim of this study was to determine epidemiology, treatment and outcome of children with first episode of NS.

Methods: This was a retrospective hospital-based cohort study in the department of pediatric nephrology of Charles Nicolle, Tunis, between 2002 and 2012. It included 52 children with idiopathic NS aged from 1 to 12 years, hospitalized for the first manifestation of the NS and followed for at least one year.

Results: The median age of presentation was 5.1 ± 2.5 years. Male to female ratio was 2.7:1. Family history of atopy was found in 14 (26.9%) patients and personal atopy was noted in 9 (17.3%) patients. Microscopic hematuria was seen in 33 (63.5%) patients. The mean blood level of albumin was 1.17 ± 4.2 g/dl, alpha-2 globulin was 1.71 ± 3.5 g/dl, cholesterol was 413.7 ± 2.4 mg/dl and the mean proteinuria was 148 ± 70 mg/kg/day. The mean time for first remission was 15.8 ± 2 days. Thirty-eight patients (73%) relapsed and 31 patients (59.6%) became steroid dependent. Total 32 (61.5%) patients recovered from their NS with average interval between the onset of illness and recovery being 3.8 ± 2.1 years (range: 2-10 years). Twenty-two (42.3%) required immunosuppressive drugs such as cyclophosphamide, mycophenolate mofetil and cyclosporine. Thirty-two patients (61.5%) were in remission and off therapy for more than 2 years. The most frequent adverse effects of steroid treatment were growth failure in 22 (42.3%) and osteoporosis in 7 (21.8%) patients. Renal functions remained normal for all patients.

Conclusion: The prognosis of idiopathic NS is good but the risk of progression to steroid dependence is high, which exposes these children to complications of long-term corticosteroid therapy. Prospective trials are necessary to identify effective and safe therapies for patients with frequent relapses and steroid dependence.

Introduction

Nephrotic syndrome (NS) is the most common glomerular nephropathy in children. Its estimated incidence is from 2 to 7 cases/100,000 children/year and its prevalence is of 16 cases/100,000 children aged under 16 years. (1-4) NS in children is idiopathic in about 90% of cases. (5-7) In 10% of cases, it is secondary to infection, systemic disease or drug intake. (1) On clinical pathology, minimal glomerular lesions are the most common findings and are found in 85% of cases (8) followed by focal and segmental hyalinosis lesions, and diffuse mesangial proliferation, which is rare in

children. (1,7,9) In minimal change disease, majority of the patients (95%) respond to corticosteroids leading to complete remission which is the steroid-sensitive form. (6,10,11) The long-term prognosis is favorable with preservation of renal function. However, two thirds of children with idiopathic NS (INS) have relapse and over half become steroid-dependent. (6,12,13) The objective of our work is to describe the epidemiological, evolutionary and therapeutic characteristics of steroid-sensitive NS in children.

Methods & Materials

A retrospective study was conducted over a period of 11 years (January 2002-December 2012) in pediatric nephrology department of the Charles Nicolle hospital in Tunis and included patients with steroid-sensitive NS (SSNS) aged 1 to 12 years. Nephrotic syndrome was defined by proteinuria > 50 mg/kg/d associated with hypoalbuminemia < 3 g/dl and hypoproteinemia < 6 g/dl. Informed consent of the parents was taken

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and study was approved by the hospital's ethics committee. Records of patients with first episode of idiopathic NS hospitalized and followed up for at least one year were analyzed. Patients who were lost to follow-up were excluded from the study. All patients were treated according to the protocol of the French Society of Pediatric Nephrology. The treatment was initially prednisone at a dose of 60mg/sqm of body surface area daily (not to exceed 60 mg/day). If NS persisted even after 4 weeks of oral prednisolone, three methylprednisolone infusions at a dose of 1 g/1.73sqm were given at 48 hours intervals. (5) Patients received 20% albumin infusion at the dose of 1 g/kg if there was severe edema, shock or hypovolemia. (5) Aspirin was given at a dose of 3 to 5 mg/kg/day to prevent thromboembolic complications in patients at risk (serum albumin <20 g/dl, fibrinogen > 6 g/l, antithrombin III <70% or D-dimer >1000 ng/ml). (5) This was followed by gradual tapering of the steroids with a total treatment duration of 4.5 months. (5) Remission was defined as proteinuria of < 4mg/kg/24 h or spot urine protein/creatinine <0.2 g/g or <0.02g/mmol) and a serum albumin >30g/l. (5) Relapse was defined as proteinuria accompanied by a clinical nephrotic syndrome and/or persistent isolated proteinuria (urine protein/creatinine higher than 1 g/g or higher than 0.11 g/mmol) for over three weeks after initial remission. Relapse was considered to be early if it occurred during tapering course of corticosteroids or within three months of stopping corticosteroid therapy. Relapses were considered to be frequent if two or more relapses occurred within 6 months following the start of the disease or if four or more relapses occurred in 1 year. (6) Steroid dependent NS (SDNS) has been defined by the International Study for Kidney Diseases in Children (ISKDC) as children with frequently relapsing nephrotic syndrome (FRNS) in whom two consecutive relapses, or two of four relapses in any 6 month period, occurred while still on a dose of steroids or within 14 days of discontinuing steroid therapy. (6,7) No patient had a kidney biopsy. Immunosuppressants such as cyclophosphamide, cyclosporine and mycophenolate mofetil were given in patients with SDNS or frequently relapsing NS when there were signs of steroid toxicity such as growth retardation defined by a height less than -2 SD, a slowdown or a break in the growth curve (8) or ocular abnormalities or pathological bone densitometry with decreased bone mineral density leading to an increased risk of fracture or psychological

intolerance. The prescribed Immunosuppressants were: cyclophosphamide in oral form at a dose of 2 to 2.5 mg/kg/day for 8-12 weeks as a single dose not exceeding 180 mg/kg cumulative dose; cyclosporine in oral form at 150 mg/sqm/day in two divided doses for 18 to 24 months; and mycophenolate mofetil in oral form at a dose of 600 mg/sqm/day in two divided doses for 12-36 months. Blood cholesterol was considered pathological if > 200 mg/dl, triglycerides were considered elevated if > 150 mg/dl. (9)

Renal function was estimated by the following equation: $0.413 \times \text{height (cm)} / \text{creatinine (mg/dl)}$ and calculated in ml/minute/1.73m². (10) Acute renal failure was defined as a rapid fall in the rate of glomerular filtration, which manifested clinically as an abrupt and sustained increase in the serum levels of urea and creatinine with an associated disruption of salt and water homeostasis. (11) The epidemiological, clinical and biological variables of the initial episode of NS as well as outcome was determined.

Statistical analysis was performed with SPSS 20.0 software. Statistical analysis of qualitative data was done using chi-square test or Fisher exact test. A p value of < 0.05 was considered as significant.

Results

Total 52 patients had idiopathic NS. The average age of patients at the time of initial presentation was 5.1 ± 2.5 years (range: 1.2 to 11 years). Six (11.5%) patients were under 2 years old, and 29 children (55.8%) were between 2 and 6 years old and remaining were above 6 years of age. Male: female ratio was 2.7:1. Consanguinity was found in 9 patients. As per seasonal trend, the first episode of NS occurred in summer in 17 (32.6%), in winter in 13 (25%), in spring in 11 (21.2%) and in fall in 11 (21.2%) patients. Five (9.6%) patients had history of renal disease in the family. Atopy was observed in the family in 14 (26.9%) patients and personal atopy was observed in 9 (17.3%) patients. A triggering factor was found in 27 (51.9%) patients of which 23 (44%) had bronchitis, 2 (2.7%) had gastroenteritis, 1 (3.7%) each had urinary tract infection due to Escherichia coli and a skin infection 2 weeks preceding the NS episode.

During the first episode, the average weight gain was 2.8 ± 0.99 kg (range: 1-5 kg). All patients had edema at admission. The average duration of edema prior to presentation was 7.1 ± 2 days (range: 1-63 days). The

Table 1. Blood protein electrophoresis

	Average rate	Minimum	Maximum
Serum albumin (g/l)	11.7 ± 2	4.2	22
Total proteins (g/l)	39.9 ± 5.5	31	56
Alpha-1 globulin (g/l)	1.5 ± 0.6	0.8	3.4
Alpha-2 globulin (g/l)	17.1 ± 3.5	9.4	29
Beta globulin (g/l)	8 ± 3	3	23.4
Beta-1 globulin (g/l)	1.8 ± 0.9	0.9	6
Beta-2 globulin (g/l)	3.1 ± 1.27	0.9	4.1
Gamma globulin (g/l)	3.3 ± 1.1	1.5	6.7

average proteinuria found on the urine dipstick test was 3.6 ± 0.5 plus (2+ to 4+). Microscopic hematuria was detected in 33 (63.5%) patients. All patients had hypoproteinemia, hypoalbuminemia and elevation of alpha-2 globulin. We found hypogammaglobulinemia in all patients except in one patient who had normal levels of gamma globulin. Table 1 reports the results of protein electrophoresis (EPP).

Renal function estimated by clearance of creatinine was normal in all patients except in one patient who presented acute renal failure caused by hypovolemia. The average plasma cholesterol level was 413.7 ± 2.4 mg/dl (range: 193.34 -595.5 mg/dl). The average plasma triglyceride was 280.7 ± 0.19 mg/dl (range: 62 to 841.4 mg/dl). The average proteinuria in 24 hours was 148 ± 70 mg/kg/day (range: 68-405 mg/kg/day). Methylprednisolone was required in 10 (19.2%) patients. Intravenous albumin infusion therapy was indicated in 11 (21%) patients due to severe edematous syndrome (7 cases), hypovolemia (3 cases) and acute renal failure secondary to relative hypovolemia (1 case). Low dose aspirin was used in 40 (76.9%) patients as anti-platelet agent. During follow-up, weight decreased by an average of 1.7 kg by day 15 of treatment and by an average of 2.4kg by day 30 of treatment. By day 15, edema disappeared in 30 (57.6%), patients, decreased in 17 patients, was stable in 4 patients, and had increased in 1 patient. By day 30, edema completely disappeared in 45 (86.5%) patients and decreased in 7 (13.4%) patients. Proteinuria disappeared by day 15 in 29 (55.7%) patients and in 43 (82.6%) patients by day 30. By day 15, normal EPP was seen in 28 (53.8%) patients. On day 30, normal EPP was seen in 42 (80.8%) patients and 10 (19.2%) patients still had abnormal EPP. The average time of the initial remission was 15.8 ± 3.2 days.

Fourteen (26.9%) patients did not have any relapse after an average follow-up duration of 20 ± 3.2 months (range: 18 to 28.8 months) whereas 38 (73%) patients had relapses. The mean interval between the initial episode and the first relapse was 5.4 ± 4 months (range: 1-24 months). The mean number of relapses per patient was 2.5 ± 1.3 (range: 1-13 relapses). Relapse was early in 32 (84.2%) patients. It was late in 6 patients with a first relapse mean time of 12.5 ± 1.6 months (range: 8-24 months). SDNS was seen in 31 (59.6%) cases, at high threshold (≥ 40 mg/kg/d) in 24 patients and at low threshold in 7 patients. Total 32 (61.5%) patients recovered from their NS with average interval between the onset of illness and recovery being 3.8 ± 2.1 years (range: 2-10 years). The mean duration of disease was 6.2 years when disease onset was between 1 and 3 years and 3.7 years when disease onset was after 3 years of age ($p = 0.001$).

Growth retardation was noted in 22 (42.3%) patients and their mean cumulative dose of prednisolone was 17048 ± 1530 mg/sqm (range: 9975- 31920). Bone density osteoporosis was found in 7 (21.8%) patients with an average cumulative dose of prednisolone being 21,090 sqm/m (range: 8060-51870). Cushing's syndrome was found in 7 (13.5%) patients with a mean cumulative prednisolone dose of 25,650 mg/sqm (range: 7980-55860). Hypertension was seen in 6 (11.5%) patients at a mean prednisolone cumulative dose of 21,730 mg/sqm (range: 7900-51870).

Immunosuppressive drugs were prescribed for 22 (42.3%) patients. The average time of introducing immunosuppressants compared to the beginning of the disease was 15.7 ± 2.3 months (range: 53-72 months) with a median of 10 months. Cyclophosphamide was used in 9 patients, mycophenolate mofetil in 7 patients, cyclophosphamide followed by cyclosporine in 1 patient, cyclophosphamide followed by mycophenolate mofetil in 4 patients, cyclophosphamide followed by cyclosporine and mycophenolate mofetil in 1 patient.

Discussion

Nearly 85% of minimal change disease starts between 1 and 10 years of age with a predilection of the school age range. (4,12) Our results are consistent with the literature data, since more than half of our patients were under 6 years during the initial episode of NS. Deschenes et al (4) linked this to the epidemiology of primary viral infections based on the age: the peak incidence of infection with the Epstein Barr Virus (EBV) is between 2 and 7 years, the prevalence of cytomegalovirus (CMV) ranges from 15-55% for pre-school children and the peak seroprevalence of adenovirus is between 3 and 5 years. This suggests that primary viral infection could be environmental agent that trigger the disease when a specific genetic background is present.

In our study, a male predominance was found. Male: female ratio is 1 in the US and 3.8 in Singapore. (4,15) In patients, where NS had begun before eight years old, male predominance is seen (14-17) as was seen in our patients who were predominantly under 6 years of age, and with advancing in age, sex ratio became approximately equal. (17) Heymann's study (18) suggested a hormonal role as puberty approaches. This suggests that the imbalance in the sex ratio in some populations evokes the involvement of one or more genes carried by the X chromosome. (19)

The frequency of the association of NS with atopy ranges from 8 to 67.7%. (18) Some studies indirectly established this link by highlighting high IgE levels in many patients with minimal glomerular lesions. (21) Other studies reported the seasonality of relapses in spring (pollen exposure) or autumn (peak incidence of mites) or the occurrence of relapses after exposure to allergens. (22) However, allergen avoidance, desensitization and use of cromolyn sodium to reduce the frequency of relapses so as to achieve remission have failed in most cases. (23) Patients with idiopathic nephrotic syndrome with minimal glomerular lesions would have a personal atopy due to an underlying abnormality of the immunological system that would predispose to both disorders rather than a causal role of atopy. (24,25) Similarly, in our patients, seasonality or atopy could not be established as an association.

A trigger of the disease is present in 28-62% of patients. (26) In our study, almost half of our patients had a trigger at the first disease outbreak. NS results from a runaway of the immune system in response to a pathogen, in particular a virus, by activating lymphocytes that would have a direct effect on the glomerulus or trigger a cascade of immunological phenomena producing circulating factors altering the glomerular barrier. (27)

Dyslipidemia is almost constant in NS. (28) Plasma concentrations of cholesterol and triglycerides increase during early nephrotic syndrome, worsen with the severity of the nephrotic syndrome and are correlated with disease activity. (28) The mechanisms of this dyslipidemia are not yet fully understood. In various studies, the average cholesterol level is above 251.35 mg/dl. (28) In our study, the average cholesterol level in the initial episode was 413.76 mg / dl and the average triglyceride level was 1166.5 mg/dl.

The treatment of idiopathic NS is based on a heavy dose of corticosteroid therapy. (29) The aim of treatment is to achieve remission in the short term, and in the long term to avoid frequent relapses or steroid dependence. The various studies report that the initial remission is achieved during the first 2 weeks in the majority of cases and that 70% of patients are in remission after 10 days of corticosteroid treatment. (30) In a French study, the median time to remission in the first episode was 11.7 days. (31) In our study, the average time of the initial remission was 15.8 days. After the first episode, about 30% of patients will permanently recover, 10-20% will relapse 3 to 4 times before recovery and 45-50% will evolve towards frequent relapses and steroid-dependence. The natural history will be towards a gradual decrease in its activity at the time of puberty. (32) The evolution towards steroid-dependence was 49% in a Japanese study (33), 52% in an Australian study (34), 56% in a Danish study (35) and 69% in a French cohort (31). In our study, we found that 59.6% of patients became steroid-dependent. The resumption of a heavy dose corticosteroid therapy at each relapse exposes patients to steroid toxicity. Growth retardation and osteoporosis are the main complications of corticosteroid therapy in children. (36) In our series, growth retardation was noted in 42.3% and osteoporosis in 21.8% patients. Concerning the impact on the size in adulthood, the literature data were controversial. (37). Hypertension occurs in 6-12% of cases. (8) In our series, hypertension occurred in 11.5% of the patients. Reviewing the literature, we found that ophthalmic complications such as cataracts or glaucoma were rare (38) and were seen during prolonged treatment and high doses of steroids. They had been reported in the Japanese series. (33) In our study, no patient had this complication.

Immunosuppressive drugs are prescribed in SDNS to prevent the occurrence of new relapses and decrease the utility of corticosteroid therapy to prevent its adverse effects. Immunosuppressants used as first line are cyclophosphamide and mycophenolate mofetil because of their lesser side effects and better tolerance. (38) Cyclosporine has renal toxicity. New Immunosuppressants used are levamisole and rituximab but they are very expensive. In our study, Immunosuppressants commonly used were cyclophosphamide and mycophenolate mofetil. No patient has relapsed under immunosuppressive drugs. The main limitation of our study lies in its design because it was a retrospective study which is inevitably a source of bias by the presence of missing data. Therefore, an underestimation of the results is possible. The other bias of our study was the small number.

In addition, some patients were followed for only one

year, and evolution towards steroid-dependence after the first year could then be underestimated. Therefore, the results should be interpreted with caution. A prospective study with a two-year follow at least would be necessary to confirm the results of our study.

Conclusion

The prognosis of idiopathic NS is good but the risk of progression to SDNS is high, which exposes these children to complications of long-term corticosteroid therapy. The identification of risk factors that lead to relapse or dependence could lead to targeted therapeutic strategies leading to minimal use of corticosteroid therapy.

Compliance with Ethical Standards

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Conflict of Interest: None

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