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Clinical Profile and Prognosis of Steroid Resistant Nephrotic Syndrome in Cameroon: A Single Centre Experience

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Abstract

Background: Steroid-resistance in idiopathic nephrotic syndrome is report high in Sub Saharan Africa. However, data on clinical profile and renal survival are scarce. We sought to compare the clinical profile of Steroid-Resistant and Steroid-Sensitive Nephrotic Syndrome (SRNS, SSNS) and evaluate the renal survival of SRNS patients in a nephrology reference centre of Cameroon.

Materials and methods: We conducted a retrospective cohort study over 7 years using clinical records of incidents patients with idiopathic nephrotic syndrome who were followed for more than 3 months. Demographic, clinical and biological data were collected. Renal survival was estimated by Kaplan and Meier curves.

Results: A total of 47 patients were included, including 27 patients with SRNS (57.4%). Age was comparable between SRNS and SSNS patients (19 [IQI 13-28] years vs. 15 [IQI 5-31] years), but the proportion of female was higher among SRNS (29.6% vs 5%, p=0.036). Delayed clinical care and impure nephrotic syndrome were more common in SRNS. Overall, 12 (44.5%) patients developed end stage renal disease and 10 (37%) died. Renal survival rates at 12, 24, 36 months were 83.3%, 33.6% and 25% respectively. Renal survival was comparable between children and adult, as well as between female and male.

Conclusion: Steroid-resistant nephrotic syndrome in common in Cameroon and it is associated with poor renal prognosis.

Keywords

Nephrotic syndrome • Steroid resistance • Renal survival • Cameroon

Introduction

Nephrotic Syndrome (NS) is a common manifestation of glomerular disease. It is the most common kidney disease in children with an annual incidence of 2-7 per 100,000 children in high income regions [1]. In adult, although less frequent, NS is also a main manifestation of glomerular disease with an annual incidence of 3 per 100,000 [2]. In both populations, idiopathic NS is usual, accounting for 80-90% of cases. Minimal Change Disease (MCD) is the leading cause of idiopathic MS in children while Membranous Glomerulopathy (MG) and Focal and Segmental Glomerulosclerosis (FSGS) are more common in adult [1-7]. Steroid sensitive NS is reported to be more common in children from Asian descent but its prognosis is good. In contrast, steroid-resistance and worse outcome have been described in Afro-American and Hispanic children [1,3,4]. In adult, steroid-resistance is more common since MCD is less frequent [2]. Increased risk of mortality and End Stage Renal Disease (ESRD) has been associated in adults and children with NS, especially among those with frequent relapses or without remission [8-10].

Idiopathic NS is also reported in Sub-Saharan Africa despite lack of epidemiological data. It may represented 3.5% to 8.6% of nephrology consultations and <1% of paediatric admissions [11-15]. It mainly affects young adults and FSGS and MCD are commonly observed [7,11,12]. Steroid-resistant NS is frequent and concerned 13-37% of children [14-21] and 15% to 40% of adults with high frequency in countries such as Nigeria, Ghana and Cameroon [7,12,22,23]. However, the renal survival of these patients is unknown. We sought to describe the clinical profile and the renal survival of patients with idiopathic Steroid-Resistant Nephrotic Syndrome (SRNS) in a Cameroonian nephrology unit.

Materials and Methods

Study design

We conducted a retrospective cohort study over a 7 year-period, from the 1st January 2013 to the 31st December 2019 in the nephrology unit of the Douala General Hospital. It is the main nephrology clinic of Douala, the most populated town of Cameroon. It also has the only public haemodialysis facility of the region.

Participants and methods

Medical records of patients with newly diagnosis NS were reviewed. All patients with idiopathic NS that were followed for least 3 months were included. Nephrotic syndrome was diagnosis by the presence of proteinuria ≥ 3+ dipstick or 3 g/day or 50 mg/kg/day and serum albumin <30 g/l in children and a proteinuria of 4+ dipstick or 3 g/g and serum albumin <35 g/l

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in adults. Patients with Chronic Kidney Disease (CKD) stage 3-5 at the first consultation were excluded. Demographic data (age, sex, and residence), clinical and biological data at diagnosis (comorbidities, past history of renal oedema, duration of symptoms before nephrologist consultation, hypertension, haematuria, kidney failure proteinuria, serum cholesterol and serum albumin), histological data, therapeutic information's and evolution on treatment were collected. Death, as well as ESRD was also noted. Adult NS criteria were used for NS diagnosed in patients of at least 15 years old, while paediatric NS criteria were used for patients under 15 years. End point for renal survival was CKD stage 5 regardless of starting dialysis. Complete remission was confirmed by a 24 hours proteinuria <0.3 g/day in three consecutive consultations with normal serum albumin and partial remission by a 24 hours proteinuria greater than 0.3 g/day but under 3 g/day with a decrease of more than 50% from baseline proteinuria. Patients were divided in two groups: Steroid-Sensitive Nephrotic Syndrome (SSNS) and Steroid-Resistant Nephrotic Syndrome (SRNS). The following definitions were used:

- SRNS was defined as absence of remission after 12-16 weeks of prednisone at 1 mg/kg/j in adult NS or in paediatric NS after 4 weeks of prednisone at 2 mg/kg/j and 3 IV bolus of methylprednisolone or 8 weeks of prednisone.
- SSN was used in patients with complete or partial remission after 12-16 weeks of prednisolone at 1 mg/kg/j in adult NS or after 4 weeks of prednisone at 2 mg/kg/j ± 3 IV bolus of methylprednisolone or 8 weeks of prednisone in paediatric NS.
- Impure NS was defined as the presence of hypertension, haematuria or renal failure at baseline in a patient with NS.
- Delayed consultation referred to first nephrology consultation more than 3 months after the beginning of the symptoms.
- Anaemia was considered when haemoglobin levels were under 10 g/dl in both children and adults.

Ethical considerations

Ethical clearance was obtained from the Ethical Board of The University of Douala. Administrative authorization from the Doula General Hospital was also obtained. Privacy of all the data collected was assured.

Statistical analysis

Clinical and biological data of SRNS and SSN were compared. Qualitative data were presented as frequency and percentage while quantitative data were presented as mean ± standard deviation or median [Interquartile Interval (IQI) 25th-75th] according to their distribution. Chi square or Fisher test was used to compare qualitative data while quantitative data were compared with Student test or its non-parametric equivalent. Renal survival was estimated by Kaplan-Meier curve and compared with Log-Rank test. The p-value was <0.05. Data were analysed with the IBM SPSS (Statistical Package for Social Sciences) version 26.0.

Results

Of the 4640 incidents patients recorded during the study period, 119 NS were noted; 49 were followed for less than 3 months and 13 had secondary NS. A total of 47 NS were included in the analysis including 20 (42.6%) SSNS and 27 (57.4%) SRNS. The incidence of idiopathic NS was 1.5%. Female were more common among SRNS (29.6% vs. 5%, p=0.036) and age was comparable between the two groups (19 [13-28] years) vs. 15 [IQI 5-31] years) (Table 1). Comorbidities were unusual, while prior episode of renal oedema was noted in one third of patients for both groups. Delayed consultation was more frequent in SRNS (29.6% vs. 5%, p=0.04). Impure NS was also more common among SRNS (81.5% vs. 45%, p=0.011) with renal failure as the main criteria (63% vs. 10%, p<0.001). Serum albumin, serum cholesterol and proteinuria were similar in both NS types (Table 2). Histology was available only in 14 patients and FSGS was the main lesion found. Duration of nephrology follow was longer in SRNS than in SSNS (20 [IQI 5-24] months vs. 7 [IQI 3-12] months, p=0.02).

All SRNS patients received nephroprotective treatment. Most patients were loss and second line treatment was started only in 41% (n=11). Cyclophosphamide were used in 29.6% (n=8) including the two patients with MG (Ponticelli regimen with cyclophosphamide and steroid); one had complete remission but relapsed after 2 years and the other progressed to ESRD and died (denied dialysis). Partial remission was also observed in two other patients. Two patients (both children) received cyclosporine. One of them progressed to ESRD and the other was switched on Mycophenolate Mofetil (MMF) with partial remission achieved. Two other patients were put on MMF with complete remission. A total of 12 (44.5%) patients developed ESRD, 6 of them (50%) were patients lost to follow up and were only readmitted with urgent need of dialysis. Ten patients died (27%), and all were in ESRD (Table 3). Death or ESRD were not observed among patients with partial or complete remission. Mean renal survival was 26.23 ± 2.8 [95% CI 20.75-31.71] months. Renal survival in children and adult were comparable (25.68 ± 4.3 [95% CI 17.2-34.16] months vs. 28.62 ± 3.8 [95% CI 21.16-36] months, p=0.89). Renal survival was also similar in both sex (male 26.16 ± 3.35 [95% CI 19.58-32.74] months, female 23.12 ± 3.43 [95% CI 16.4-29.84 months, p=0.95) (Figures 1-4).

Table 1. Demographic and baseline clinical and biological data.

Variables	Steroid-sensitive nephrotic syndrome (%) n=20	Steroid-resistant nephrotic syndrome (%) n=27	p-value
Sex			
Male	19 (95)	19 (70.4)	0.036
Female	1 (5)	8 (29.6)	
Age			
Median [IQI] (Years)	15 [5-31]	19 [13-28]	0,86
Paediatric NS	10 (50)	10 (37)	0,27
Adult NS	10 (50)	17 (63)	
Residence			
Rural or semi-rural	5 (25)	7 (26)	0.9
Urban	15 (75)		
Comorbidities			
None	19 (95)	26 (96,3)	0,94
Hypertension	1 (5)	1 (3,7)	
Prior renal oedema	7 (35)	10 (37)	0,56
Alternative therapy	6 (30)	13 (48)	0,17
Duration of symptom (weeks) Median [IQI]	2 [1-4]	4 [2-8]	0.022
Clinical sign			
Oedema	20 (100)	27 (100)	-
Anasarca	8 (40)	14 (52)	0,3
Hypertension	7 (35)	11 (40.7)	0.52
Biological signs			
Serum albumin <20g/l	8 (40)	11 (40.7)	0.49
Anaemia	2 (10)	8 (30)	0.19
Renal failure	2 (10)	17 (63)	<0.001
Haematuria	0 (0)	5 (8)	-
Impure NS	9 (45)	22 (81.5)	0,011
Histology (n=14)			
MCD	1	1	-
FSGS	1	9	
MG	0	2	
MPGN	0	1	

Note: IQI: Interquartile Interval; MCD: Minimal Change Disease; FSGS: Focal and Segmental Glomerulosclerosis; MPGN: Membrane-Proliferative glomerulonephritis; MG: Membranous Glomerulopathy

Table 2. Clinical and biological data at baseline.

Variables	Steroid-sensitive nephrotic syndrome n=20	Steroid-resistant nephrotic syndrome n=27	p-value
Clinical signs			
Weight (kg) Median [IQI]	57 [20-71]	60 [46-83]	0.86
PAS (mmHg) Mean ± standard deviation	129 ± 21.33	129 ± 21.2	0.99
PAD (mmHg) Mean ± standard deviation	79.64 ± 12.86	81.58 ± 12.27	0.64
Biological signs			
Serum albumin (g/l)	17.36 [13-23.5]	19.4 [12.4-29.5]	0.88
Median [IQI]			
Serum cholesterol (g/l)	4.5 [3.56-6.12]	4.9 [3.68-6.87]	1
Median [IQI]			
Haemoglobin level (g/dl) Median [IQI]	12.5 ± 2.37	11.4 ± 3.22	0.29
Creatinine (mg/dl)	0.64 [0.4-1.2]	1.55 [0.5-2.8]	0.011
Median [IQI]			
24h proteinuria (g/24h) Median [IQI]	3.08 [2,3-11.2]	5.94 [2.3-7.2]	0.62
Serum sodium (mmol/l) Mean ± standard deviation	134.8 ± 7.1	136.4 ± 7.8	0.614
Serum potassium (mmol/l) Median [IQI}	4.1 [3.88-4.8]	4.3 [3.6-4.9]	1
Note: IQI: Interquartile Interval			

Table 3. Therapeutic data and outcome.

Variables	Effective (n=27)	Percentage
Treatment option		
Cyclophosphamide	8	29.5
MMF	3	11.1
Cyclosporine	2	7.4
Evolution		
Remission	5	18.5
Absence de remission	20	74
Death	10	37
End stage kidney disease	12	44.5
Loss of view	8	29.5
Note: Complete remission n=2; Partial remission n=3		

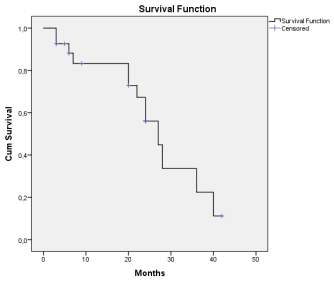

Figure 1. CT scan with contrast showing inflammation in wall of aorta and Morita class III coeliac trunk anomaly.

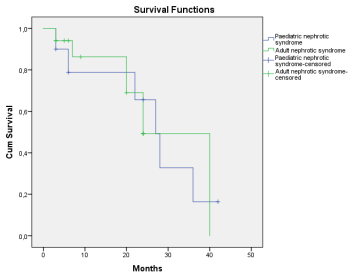

Figure 2. Renal survival according to age (p=0.89).

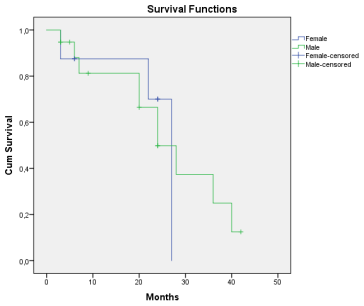

Figure 3. Renal survival according to sex (p=0.95).

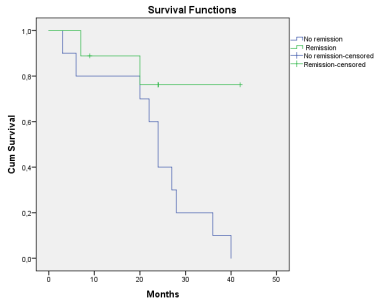

Figure 4. Renal survival according to remission (p=0.054).

Discussion

The aim of this study was to compare the clinical profile of SRNS with SSNS and determine renal survival of patients with SRNS. The incidence of idiopathic NS was 1.5% and SRNS was noted in 57.4% (children 50%, adult 63%). Clinical profile of SRNS was similar to SSNS; however, delayed consultation and baseline renal failure were more common in CSRNS. FSGS were the main histology lesions observed in CSRNS. Ten patients (27%) died and 12 patients (44.5%) reached ESRD with a mean renal survival of 26.23 ± 2.8 months. At 36 months, renal survival was 25%.

Steroid-resistance was common in our series and concerned more than half of the patients. This high rate of steroid resistance was found in children (50%) as well as in adults (63%). Similarly, Ashuntantang et al. previously reported that in Cameroon, 40.6% of idiopathic NS were steroid resistant [23]. To our knowledge, no study on the frequency of steroid resistant NS in children has been conducted in Cameroon before. The observed high rate of corticosteroid resistance in both adult and children has also been reported in other Sub-Saharan countries such as Nigeria, Ghana and South Africa [19,21,22,24] and probably reflects the high prevalence of FSGS in African populations due to genetic predisposition such as polymorphism in the ApoL1 gene. Indeed, FSGS were the most common histological lesion observed in SRNS in our series as described by other authors [19,24].

The clinical profile of SRNS was marked by late nephrologist consultation and frequent renal failure compare to SSNS. Renal failure is usually seen in SRNS, especially among those with FSGS [23,25]. Asinobi et al. in Nigeria, also noted that duration of symptoms was longer in mSRNS (3 months vs. 1 month), although the difference was not significant. In our practise, since nephrology service is not universally available, the diagnosis of NS is sometimes already suspected in first health facilities and corticosteroid initiated. The patient are then referred to the nephrologist when no response if observed. This could explain the delay of nephrology consultation and also contribute to the high rate of corticosteroid resistance observed in the nephrology unit since patients who respond to corticosteroid are not referred.

SRNS is associated with poor renal outcome, especially if remission could not be achieved. In the Podo Net registry, 10 years renal survivals of SRNS children with SRNS with partial or complete were 94% and 43% respectively [26]. In our series, the overall renal survival at 3 years was 25%. However, poor outcome was not observed in patient in remission. Access

to immunosuppressive agents such as cyclosporine, MMF or Rituximab is difficult in our context since they are very expensive or not available. As remission was associated with good outcome, better prognosis could have been obtained if they were more available. Another problem is the uses of traditional remedies. Most of the lost patients went to traditional healers and considered their disease as spiritual origin. Nephroprotective treatments are then stopped and traditional remedies with potential nephrotoxicity are used which could contribute to the rapid development of ESRD.

Conclusion

Steroid–resistant NS is common in our settings. Clinical profile of SRNS is marked by late nephrologist consultation and baseline renal failure. It is associated with poor clinical outcome, especially in the absence of remission.

Conflict of Interest

The authors declare no conflict of interest

Limits

This study has some limits. Because of its retrospective nature, selection bias is possible and could contribute to high rate of corticosteroid resistance since these patients have longer duration of nephrology follow. Our sample size is also relatively small. Finally, as it is a monocentric study, our result may not be reflective of NS frequency in Cameroon.

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