

Research Article

The Triggers and Patterns of Relapse in Childhood Idiopathic Nephrotic Syndrome: A Retrospective, Descriptive Study in a Tertiary Hospital, South-East Nigeria

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Abstract

Background: Globally, acute respiratory infection (ARI) and urinary tract infection (UTI) are the predominant infectious triggers of relapse in idiopathic nephrotic syndrome. In the West African sub-region, most studies on the syndrome have focused essentially on the clinical features, steroid sensitivity and histology patterns.

Aim: The present study aims to determine the triggers and patterns of relapse in Nigerian pediatric patients with idiopathic nephrotic syndrome.

Subjects and Methods: A retrospective analysis of the case notes of 30 patients with idiopathic nephrotic syndrome was conducted using a structured proforma. Data were analysed with the Statistical Package for Social Sciences (SPSS) version 17.0. Variables were expressed in frequencies and proportions (percentages). Chi-square test and Spearman's rank correlation coefficient for non-parametric analysis were applied as appropriate, and p value of less than 0.05 was adopted as the level of statistical significance.

Results: The most common identified trigger of relapse was UTI, which was recorded in 12/30 (40.0%) of the patients. ARI and malaria infection ranked second on the list of trigger factors: each documented in 7/30 (23.3%) of the patients. Non-compliance to drugs was noted in 1/30 (3.3%) while no trigger factor was identified in 3/30 (10.1%) of the patients. On the whole, infrequent relapses were seen in 16/30 (53.4%) of the patients, frequent relapses in 10/30 (33.3%), while 4/30 (13.3%) had no recorded relapses. The patterns were not significantly influenced by the patients' age ($p=0.479$), and socio-economic class ($p=0.918$), and the type of initial treatment regimen ($p=0.829$).

Conclusions: Frequent relapses still remain a challenge in the management of nephrotic syndrome. Infectious triggers constitute a major cause of relapse; and malaria may be an unrecognized trigger in the tropics. Relapse-specific interventions may have to be expanded to include malaria chemoprophylaxis such as intermittent preventive therapy, particularly for nephrotic patients in the tropics where malaria appears endemic.

ABBREVIATIONS

UTI: Urinary Tract Infection; ARI: Acute Respiratory Infection; MAL: Malaria

INTRODUCTION

Nephrotic syndrome (NS) refers to the constellation of massive proteinuria, hypoalbuminemia, generalized oedema and hyperlipidemia due to failure of the glomerular filtration barrier [1]. The syndrome in children is commonly caused by either of two idiopathic diseases: minimal-change nephropathy (MCN) and focal segmental glomerulosclerosis (FSGS) [1]. According to a report by the International Study of Kidney

Disease in Children (ISKDC), a vast majority of pre-adolescent children with idiopathic NS present with MCN on renal biopsy [2]. This histological subtype had previously been documented as the most common cause of childhood nephrotic syndrome [3]; more than 90% of affected children achieve remission with oral corticosteroids and are identified as having steroid-sensitive NS (SSNS) [4,5]. The disease progresses to frequent relapses, often accompanied by steroid dependence in about 20% to 60% of patients [6]. The majority of children with FSGS have steroid-resistance, as only 20% respond to corticosteroids with a high risk of developing end-stage renal disease [7]. Thus, the main treatment challenges in idiopathic NS are steroid resistance, frequent relapses and steroid dependence [8].

In the West African sub-region, the histological patterns appear to vary in different countries. For instance, one retrospective study in Ghana reported FSGS and MCN as the predominant pattern in children [9], while in Senegal, MCN, FSGS and membrano proliferative glomerulonephritis (MPGN) were observed as the most frequent types in that order [10]. By contrast, other authors documented a high proportion of cases with MPGN and quartan malaria nephropathy (QMN) among Nigerian children in the 1980s [11] and MPGN in the 1990s [12]. Specifically in northern Nigeria, one study noted a preponderance of QMN in Kaduna [11], while another study reported FSGS as the predominant histological diagnosis in Kano [13]. However, in a more recent report in south-west Nigeria, some investigators suggested that FSGS was the most common histology followed by MPGN [14]; their findings underscore the changing trend in the histology patterns of NS. For instance, QMN which used to be a common pattern in some parts of Nigeria has now been reported as a rare or non-existent entity [15,16].

The common patterns of relapse in SSNS consist of infrequent relapses, frequent relapses, and steroid dependence [17,18]. Predictors of frequent relapses and steroid dependence include age younger than 3 years at onset, male gender, a history of a topy, delayed time to remission (after 7-9 days), and occurrence of an early relapse (in the first 6 months after initial treatment) [19-25].

Both infectious and non-infectious triggers of relapse have been reported in several studies [26-31]. Among the documented infectious triggers, viral acute respiratory tract infection (ARI) consistently ranks as the most prominent and frequent factor globally [26-32]. On the other hand, urinary tract infection (UTI) predominates as the infectious trigger in other studies [29-31]. All these studies [26-31] were conducted outside Africa. Furthermore, most studies on idiopathic nephrotic syndrome in Nigerian children have essentially reported about the clinical features, response to steroids and histology patterns [11-16,33-39]. To the best of the authors' knowledge, none has reported about the triggers of relapse in this clime. The present study was thus conducted in a south-east Nigerian setting to determine the triggers and patterns of relapse in paediatric patients with idiopathic nephrotic syndrome. Targeted interventions based on identified triggers will reduce relapses and ameliorate disease morbi

Subjects and methods

A retrospective analysis of the case notes of 30 patients with idiopathic nephrotic syndrome was conducted between May and June 2013. The diagnosis was based on the tetrad of 'nephrotic-range' proteinuria, hypoalbuminuria, generalized edema, and hyperlipidemia [1]. 'Nephrotic-range' proteinuria refers to proteinuria of $\geq 3+$ on dip-stick urinalysis or 'spot urine' protein (urine protein/creatinine ratio of > 2000 mg/g) [18].

Inclusion criteria: The patients were enrolled for the study if

a. They had been attending the Pediatric Nephrology Clinic of the University of Nigeria Teaching Hospital Enugu 12 months prior to the commencement of the study

b. They had primary or idiopathic nephrotic syndrome.

Exclusion criterion:

a. Patients with secondary nephrotic syndrome were excluded.

After ethical approval from the Health Research and Ethics Committee (HREC) of the University of Nigeria Teaching Hospital Enugu, the following data were retrieved from the case notes of the patients using a structured Proforma:

1. Bio data which included the age of the patients at first presentation to the clinic, the current age at the period of the study, the gender, and social classification using the method proposed by Oyedele [40].
2. Presenting clinical features on first contact and initial diagnosis
3. Presence of clinical parameters like microscopic hematuria and hypertension
4. Initial laboratory findings
5. Number of renal biopsies done, and the histopathological diagnoses
6. Initial medications (treatment regimens) after first contact, and medications (treatment regimens) on subsequent contacts
7. Response to treatment regimens: remission (the onset and duration), and the patterns of relapse
8. Identified trigger factors of relapse (established from historical documentation and laboratory records). A factor is suspected to be a trigger if it preceded or concurrently occurred with recorded episodes of relapse. For instance, the diagnosis of possible triggers like UTI was made using clinical features and positive nitrite/ leucocyte esterase tests on dipstick urinalysis, as well as positive urine culture. Plasmodium falciparum malaria was identified as a trigger factor based on positive blood film and presumptive malaria symptomatology and signs
9. Response of relapses to therapeutic interventions

Definition of terms: Microscopic hematuria is defined as the presence of more than 5 red blood cells/high power field in a centrifuged urine specimen [41].

Hypertension is defined as systolic or diastolic blood pressure values above the 95th percentile for age, gender and height [42].

Remission refers to nil or trace proteinuria < 30 mg/dl for 3 consecutive days after commencement of treatment [43].

Relapse means recurrence of 100 mg/dl ($\geq 2+$) proteinuria for ≥ 3 consecutive days after having been in remission [43].

Frequent relapses refer to two or more relapses within 6 months of initial response or ≥ 4 relapses in any 12-month period [43].

Infrequent relapses refer to ≤ 3 relapses within any 12-month period [18].

Statistical analysis: Data relevant to study the objectives were analysed using the Statistical Package for Social Sciences

(SPSS) version 17.0. Variables were expressed in frequencies and proportions (percentages). Chi-square test and Spearman's rank correlation coefficient for non-parametric analysis were applied as appropriate, and p value of less than 0.05 (< 0.05) was adopted as the level of statistical significance.

RESULTS

Socio-demographic characteristics of patients

As shown in Table 1, 11/30 (36.7%) of the children were aged between 6 to 10 years while 11/30 (36.7%) were aged 11 to 15 years at first clinical documentation. Their age distribution at the time of study showed similar pattern of frequencies (each of the age groups- 6 to 10 years and 11 to 15 years- constituted 30% of the total patients). On the whole, there was a slight male predominance with male/female ratio of 1.3:1. About 4/30 (13.3%), 14/30 (46.7%), and 12/30 (40.0%) belonged to lower, middle and upper socio-economic classes respectively.

Histopathological sub-types

At the period of study, only 7/30 (23.3%) of our patients had undergone renal biopsy. Among the seven patients, the following histo-pathological sub-types were reported: focal segmental glomerulosclerosis [FSGS] 2/7 (28.6%), minimal change nephropathy [MCN] 2/7 (28.6%), membrano proliferative glomerulonephritis [MPGN] 2/7 (28.6%), and diffuse hypercellularity 1/7 (14.2%).

Triggers and patterns of relapse

In Figure 1, the most common identified trigger of relapse was urinary tract infection (UTI): noted in 12/30 (40.0%) of the patients. The diagnosis of UTI was made using clinical features and positive nitrite/ leucocyte esterase tests on dipstick urinalysis in 7/12 (58.0%) of the patients, while 5/12 (42.0%) had positive urine culture. Acute respiratory infection (ARI) and malaria infection ranked second on the list of trigger factors: each

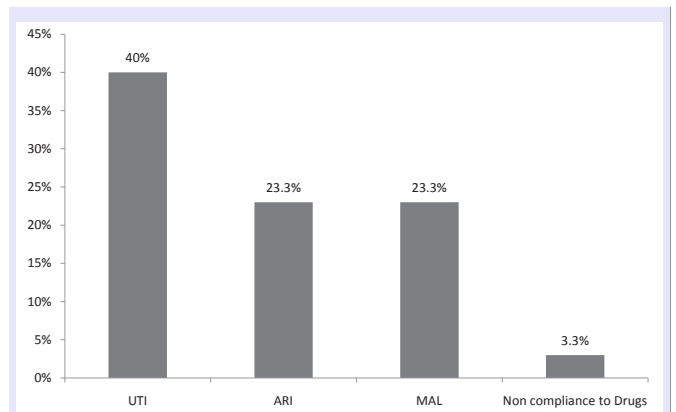


Figure 1 Frequency of identified triggers of relapse.

Abbreviations: UTI: Urinary Tract Infection; ARI: Acute Respiratory Infection; MAL: Malaria

documented in 7/30 (23.3%) of the patients. Non-compliance to drugs was noted in 1/30 (3.3%) while no trigger factor was identified in 3/30 (10.1%) of patients. Plasmodium falciparum malaria was recorded in 6/7 (82.0%) of the patients based on positive blood film; presumptive diagnosis was made on only 1/7 (18.0%) based on malaria symptomatology and signs

In summary, infrequent relapses were seen in 16/30 (53.4%) of the patients, frequent relapses in 10/30 (33.3%), while 4/30 (13.3%) had no recorded relapses. As illustrated in Table 2, these patterns were not significantly influenced by the patients' socio-demographic variables like age ($p=0.713$), gender ($p=0.789$) and socio-economic class ($p=0.690$)

Initial treatment regimen versus patterns of relapse

We usually adopted the following initial treatment regimens based on associated clinical and laboratory features such as hypertension, derangement in serum electrolyte, urea and creatinine, and microscopic hematuria. Thus, some patients received (i) *steroid alone* on first contact (based on these criteria: age bracket for MCN, absence of hypertension and hematuria, as well as normal serum electrolyte, urea and creatinine); (ii) *angiotensin-converting enzyme inhibitor (ACEI) alone* such as enalapril or lisinopril; or (iii) *ACEI plus steroid* for patients within the age bracket for MCN associated with only hypertension; (iv) *cyclophosphamide alone* for those outside the age bracket for MCN who also had hypertension, hematuria and derangement in serum electrolyte, urea and creatinine; and (v) *steroid plus cyclophosphamide* for those within the age bracket for MCN but with hypertension, hematuria and derangement in serum electrolyte, urea and creatinine. As shown in Table 3, all the patients on either ACEI alone or on steroid plus cyclophosphamide had only infrequent relapses; those on cyclophosphamide alone showed only frequent relapses; 9/17 (52.9%) of those on steroid alone had infrequent relapses with 5/17 (29.4%) showing frequent relapses and 3/17 (17.7%) with no recorded relapses. For those on steroid plus ACEI, 5/10 (50.0%) had infrequent relapses while 4/10 (40.0%) had frequent relapses; only 1/10 (10%) had no documented relapses. The patterns of relapse were not significantly affected by the type of initial treatment regimen ($p=0.829$).

Table 1: Socio-demographic characteristics of the patients.

Variable	Frequency	Percentage
Age (years)*		
1-5	6	20.0
6-10	11	36.7
11-15	11	36.7
16-20	2	6.6
Current age (years)†		
1-5	2	6.7
6-10	9	30.0
11-15	9	30.0
16-20	7	23.3
21-25	3	10.0
Gender		
Male	17	56.7
Female	13	43.3
Socio-economic class‡		
Lower (classes IV & V)	4	13.3
Middle (classes III)	14	46.7
Upper (classes I & II)	12	40.0

*Age at first documentation

†Age at the time of study

‡Classification based on the method proposed by Oyediji [25].

Table 2: Relationship between patterns of relapse and socio-demographic variables.

Variable	Patterns of relapse		Spearman's rank correlation coefficient	P value
	Infrequent N (%)	Frequent N (%)		
Age at first contact				
1-5 years	3 (10.0)	3 (10.0)	-0.145	0.444
6-10 years	6 (20.0)	3 (10.0)		
11-15 years	5 (16.7)	4 (13.3)		
16-20 years	2 (6.7)	0 (0.0)		
Current age*				
1-5 years	1 (3.3)	1 (3.3)	0.134	0.479
6-10 years	4 (13.3)	3 (10.0)		
11-15 years	5 (16.7)	3 (10.0)		
16-20 years	5 (16.7)	1 (3.3)		
21-25 years	1 (3.3)	2 (6.7)		
Socio-economic class†				
Lower	3 (10.0)	1 (3.3)	-0.020	0.918
Middle	6 (20.0)	5 (16.7)		
Upper	7 (23.3)	4 (13.3)		

*Age at the time of study †Based on the classification by Oyediji [25]

Table 3: Initial treatment regimen versus patterns of relapse.

Initial treatment regimen*	Patterns of relapse			X ²	p value
	No relapse n (%)	Infrequent relapses n (%)	Frequent relapses n (%)		
ACEI alone	0 (0.0)	1 (100.0)	0 (0.0)	4.304	0.829
Steroid alone	3 (17.7)	9 (52.9)	5 (29.3)		
Cyclophosphamide alone	0 (0.0)	0 (0.0)	1 (100.0)		
Steroid + ACEI	1 (10.0)	5 (50.0)	4 (40.0)		
Steroid + Cyclophosphamide	0 (0.0)	1 (100.0)	0 (0.0)		

ACEI- angiotensin-converting enzyme inhibitor

*Treatment regimen instituted at first contact

DISCUSSION

In the current study, infectious triggers of relapse predominate over the non-infectious and idiopathic triggers. This observation is consistent with the reports from previous studies [26-32]. For instance, in a retrospective study in a health facility in Pakistan, Moorani reported infections, poor drug compliance and idiopathic factors in 62.9%, 10.4% and 26.7% of the patients respectively [26]. In his study, ARI constituted 54.5% of the infectious triggers; diarrhea 22.3%, UTI 8.2% and other infections 15.0%. In contrast, our study documented UTI as the predominant infection followed by ARI and possibly malaria. The predominance of UTI over other infections has also been reported by other workers [30,31]. Elsewhere in Canada, McDonald et al in a prospective study reported ARI as the cause of relapse in 69.0% of the cases [27], while Takahashi et al in a retrospective study in Japan documented ARI as the trigger in 52.0% of relapses [28]. Similarly, Gulati et al in a prospective study in India noted upper respiratory infection in an overwhelming 92.0% of the cases [29]. In most of the series, it is obvious infections are the more frequent causes of relapse in nephrotic syndrome. Interestingly, malaria infection has been noted as a concomitant factor in 23.3% of our patients. We speculate that its association with relapses may either be causal as it may be a hitherto unrecognized trigger factor or casual making it an incidental finding.

The pathogenesis of nephrotic syndrome revolves around the 'immune dysregulation' hypothesis; the infectious triggers of relapse have been linked to cytokine release [27]. A type 2 cytokine bias is reported in patients with MCN [44]. Presentation of antigens to T lymphocytes results in a polarized immune response namely type 1 (dominated by interleukin 2) and type 2 (dominated by interleukins 4, 10 and 13). In vitro studies suggest that podocytes express receptors for interleukin-4 and interleukin-13; activation of these receptors by the respective cytokines might disrupt glomerular permeability leading to proteinuria [45]. Thus, we suggest that the role of malaria as a possible trigger of relapse can be explained by the immediate 'non-specific' immune response induced by acute malarial infection, although the humoral or cellular mechanisms are poorly defined [46]. Nevertheless, natural killer cells induce the production of the pro-inflammatory cytokine, interleukin-8, which in turn helps in the recruitment and activation of other cells during malaria infection [46]. Other immunological processes results in the elaboration of cytokines such as interleukin-10 and transforming growth factor- β (TGF- β) which negatively control both innate and adaptive responses. Specifically, elevated TGF- β 1 production might trigger the expression of integrin-linked kinase (ILK), a protein which is related to the pathogenesis of many nephropathies associated with proteinuria

[47]. The upregulation of ILK in the podocytes may determine the occurrence of epithelial-mesenchymal transition (EMT) in these cells [47]; these changes may damage the glomerular filtration barrier resulting in proteinuria [48].

Secondly, this study has shown that the following histology patterns were common in our biopsied patients albeit few in number- FSGS, MPGN and MCN. This finding agrees with the trend from reports in other parts of the country [12-14], as well as in other countries within the West African sub-region [9,10]. It varies with the documented preponderance of MCN seen in Caucasian children [4,5]. Global reports nevertheless indicate variations in the prevalence rates of these major histopathologic subtypes. Interestingly, each histology lesion associated with idiopathic nephrotic syndrome appears to play a role in steroid responsiveness and relapses [2]. Although almost 80% of children diagnosed with nephrotic syndrome in a multicenter International Study of Kidney Diseases in Children (ISKDC) study entered remission following an initial 8-week course using prednisone, when these children were analyzed based on histology, steroid responsiveness was found in 93% of those with MCN compared with only 30% of those with FSGS and 7% of those with MPGN [2]. Thus, relapses and steroid dependence are expectedly prominent in MCN while FSGS and MPGN are associated with steroid resistance [8].

In our study, relapses were documented in 86.7% of the reviewed patients; only 13.3% had no recorded relapses. Infrequent relapses appeared to be the commoner pattern as was observed in 53.4% of the patients, while 33.3% had frequent relapses. It is not surprising since majority of our patients presumably had SSNS; about 57.0% and 33.3% of them were placed on steroid and steroid plus ACEI respectively as the initial treatment regimen. These findings are in keeping with the observation that relapses occur in 60.0%-90.0% of children with SSNS who are initial responders [49-51]. Generally, about 50.0%-60.0% of children with SSNS have frequent relapses or steroid dependence [18]. Our findings are also in tandem with those of a study in India which show that about 64.2% of patients with SSNS were frequent relapsers while 35.8% had infrequent relapses [51]. Furthermore, there was no significant influence of variables like age, gender and socio-economic status on the patterns of relapse which differs with previous reports about predictors of frequent relapses and steroid dependence [19-25].

The challenges in treating SSNS have resulted in the use of long-term immunosuppressive drugs and steroid-sparing strategies such as cyclophosphamide, calcineurin inhibitors (cyclosporine A and tacrolimus), mycophenolate mofetil (MMF), and low-dose alternate day prednisolone [52], as well as interventions to reduce rates of relapse like zinc supplementation [53,54], and initiating corticosteroid or its dose-adjustment during ARI episodes [32,55-57]. The Kidney Disease: Improving Global Outcomes (KDIGO) group recommends a daily administration of prednisolone during episodes of upper respiratory tract and other infections in order to reduce the risk for relapse in children with frequently relapsing and steroid dependent SSNS already on alternate day prednisolone [58]. Obviously, these relapse-specific interventions can reduce the morbidity associated with frequent or infrequent relapses, and ultimately improve the child's quality of life [52].

Given the possible role of malaria infection as a trigger of relapse from our study findings, then its targeted intervention may help to reduce the morbidity of nephrotic syndrome. We suggest an intervention like intermittent preventive therapy or treatment (IPT), which is a public health intervention aimed at treating and preventing malaria episodes in infants (IPTi), children (IPTc), schoolchildren (IPTsc) and pregnant women (IPTp). The intervention is based on two tested malaria control strategies namely clearance of existing parasites (treatment effect seen in mass drug administration's) and prevention of new infections (prophylaxis). In IPTc and IPTsc, the monthly administration of combinations of sulphadoxine/pyrimethamine (SP) and artesunate [59], as well as SP and camoquine [60] have been proven to be effective in reducing malaria attacks. Since idiopathic NS usually occurs in the pre-adolescent age group, we recommend these subtypes of IPT in our nephrotic children to reduce relapse-specific morbidity.

Finally, the current study has also noted that the patterns of relapse were not significantly influenced by the initial treatment regimen. This is in keeping with the previous observation that treatment duration rather than treatment regimen is linked with frequent relapses [61]. The only predictors of frequent relapses documented in the literature are longer time to first remission and shorter time from remission to first relapse [62,63], while remission status at 6 months after initial presentation is a predictor of infrequent relapses [63].

Study limitations

As a retrospective study, inaccurate record keeping in case notes, selection and information biases and the relatively small sample size may have affected data accuracy and thus the overall veracity of the findings. For instance, it is difficult to make any objective conclusion from comparing the initial treatment regimen with patterns of relapse because of the small sample size. As at the time of the study, only few of our patients had been biopsied for histopathological diagnosis; it was partly due to initial paucity of expertise and resources for the procedure, as well as the criteria adopted for enlisting the patients for biopsy.

CONCLUSIONS

Infectious triggers of relapse predominate over the non-infectious triggers. UTI appears to be the most common trigger of relapse in childhood idiopathic NS in our series. There may be a causal association between malaria infection and episodes of relapse noted in some patients, a finding hitherto undocumented. ARI which ranked second to UTI in this series remains a well-recognized trigger of relapse. Frequent and infrequent relapses still remain a challenge in the management of idiopathic nephrotic syndrome, especially SSNS. Relapse-specific interventions may have to be expanded to include malaria chemoprophylaxis such as IPT, particularly for nephrotic patients in the tropics where the infection is endemic.

AUTHORS' CONTRIBUTIONS

SNU conceptualized the study and designed the protocol. CIE collected the data. SNU drafted the initial manuscript. CIE, HUO and OIO revised the manuscript. All the authors read and approved the final draft.

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