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Research Article

Triggers, Duration of Therapy and Sedimentation Rate in Children with Nephrotic Syndrome

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Abstract

Aim: Triggers, duration of daily corticosteroid therapy and the role of Erythrocyte Sedimentation Rate (ESR) in children with Idiopathic Steroid Sensitive-Nephrotic Syndrome (SSNS) were evaluated.

Methods: 40 episodes (9 initial episodes and 31 relapses) of idiopathic SSNS in 9 children were evaluated (2 had FSGS, 5 minimal change diseases). Data are presented as average +/- standard deviation. Different subgroups were compared with student's t-test and equality of variance tested with F-test.

Results: All of the 9 initial episodes and only 58.1 % of relapses were triggered by acute, mostly afebrile respiratory tract infections. Duration of daily corticosteroid therapy was shorter in patients with Steroid-Dependent Nephrotic Syndrome (SDNS) compared to other patients (14.5 +/- 7.6 vs. 24.7 +/- 6.8 days, p=0.071) and shorter in small children with Body Surface Area (BSA) < 1 m^2 compared to children with BSA > 1 m^2 (14.8 +/- 9.8 vs. 26.7 +/- 18.9 days, p = 0.058) but the difference did not reach statistical significance. Average ESR was 71,6 +/- 30,5 mm/h in initial episodes compared to 20,5 +/- 23,8 mm/h in relapses (p = 0.000058). The correlation coefficient between time to achieve remission and ESR was 0.09.

Conclusion: Children with initial episodes of SSNS had higher proportion of triggers as well as higher ESR compared to relapses. There was no correlation between time to achieve remission with daily corticosteroid therapy and ESR or between histology result of renal biopsy and clinical course of SSNS.

Keywords: Triggers; Erythrocyte sedimentation rate; Steroid sensitive-nephrotic syndrome; Initial episodes; Relapses

Introduction

Idiopathic nephrotic syndrome is the most common glomerular disease of childhood, representing approximately 90 % of children with nephrotic syndrome. It includes three histologic types: Minimal Change Disease (MCD), mesangial proliferation and Focal Segmental Glomerulosclerosis (FSGS). MCD is the most common among them, representing about 85 % of cases. The initial episode and subsequent relapses may follow minor infections and, sometimes, insect bites, bee stings or poison ivy [1]. Over 90 % of children with MCD respond to corticosteroid therapy and over 70 % among them subsequently develop a relapsing course. Response to corticosteroid therapy is the most important factor in determining prognosis since a good response to this therapy is ssociated with a low risk of developing chronic kidney disease [2]. The purpose of this retrospective study was to analyse the triggers (triggering events) of idiopathic nephrotic syndrome as well as duration of daily corticosteroid therapy needed to achieve remission. I analysed this in different subgroups of these patients, such as patients with Steroid Dependent Nephrotic Syndrome (SDNS), defined as having relapses whilst on steroid therapy or within 14 days of its discontinuation [2], and also in patients of different sizes. The role of Erythrocyte Sedimentation Rate (ESR) in Steroid Sensitive-Nephrotic Syndrome (SSNS) was also evaluated because following levels of ESR over time is useful in monitoring the state of some rheumatic diseases [3] that also affect the kidneys.

Materials and Methods

40 episodes of idiopathic SSNS in 9 children between years 2009 and 2013 were evaluated. There were 9 initial episodes and 31 relapses among them. Table 1 presents clinical characteristics of patients included in the study. I analysed triggers, time to achieve remission with daily corticosteroid (1 mg/kg of methylprednisolone) therapy (in days) and Erythrocyte Sedimentation Rate (ESR, in mm/h) in all episodes of nephrotic syndrome as well as in different subgroups. The subgroups analysed and compared were patients with SDNS vs. others, initial episodes of nephrotic syndrome vs. relapses and small children with Body Surface Area (BSA) < 1 m^2 vs. children with BSA > 1 m^2. BSA in children was calculated according to Mosteller formula: $BSA\ (m^2) = \sqrt{\frac{Height(cm) \times Weight(kg)}{3600}}$ [4].

Statistical Analysis

Time to achieve remission with daily corticosteroid therapy and ESR are presented as average +/- standard deviation. Different subgroups were compared statistically with student's t-test and equality of variance tested with F-test. The correlation between time to achieve remission and ESR was also analyzed and presented as correlation coefficient. Data were collected and statistical analysis was

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Table 1: Clinical characteristics of patients included in the study.

Patient No.	Sex	Age at onset (years)	Histology result (if renal biopsy indicated)	Clinical response to corticosteroids	No. of relapses	Drugs used
No. 1	Girl	14,3	FSGS - tip variant	FRNS	2	MMF
No. 2	Boy	5,2	MCD - IgM nephropathy	FRNS	3	MMF
No. 3	Girl	4,8	MCD (6% FSGS)	SDNS	9	MMF, Levamisole
No. 4	Boy	4,8	MCD	FRNS	3	MMF
No. 5	Girl	1,3	Biopsy not indicated		1	
No. 6	Girl	12,0	FSGS		0	
No. 7	Girl	3,5	MCD *	SDNS	6	MMF, Levamisole
No. 8	Girl	6,9	MCD - IgM nephropathy	SDNS	7	MMF, CYPH
No. 9	Boy	3,0	Biopsy not indicated		0	

Abbreviations: MCD: Minimal Change Disease; FSGS: Focal Segmental Glomerulosclerosis; FRNS: Frequently Relapsing Nephrotic Syndrome; SDNS: Steroid Dependent Nephrotic Syndrome; Drugs used – in addition to corticosteroids; MMF: Mycophenolate Mofetil; CYPH: Cyclophosphamide; MCD * - minimal change disease with diffuse mesangial proliferation, severe acute mixed cellular tubulointerstitial nephritis with signs of nephrocalcinosis; this patient was given a homeopathic remedy (Lycopodium extract) before admission to the hospital due to third relapse that was complicated with a culture-negative peritonitis.

Table 2: Triggers of idiopathic Steroid-Sensitive Nephrotic Syndrome (SSNS) in children.

Trigger:	Acute infection (mostly viral)	Other triggers	No trigger	Combined
Initial episodes	9 (100 %)	0	0	9 (100 %)
Relapses	18 (58,1 %)	3 (9,7 %)	10 (32,3 %)	31 (100 %)
All episodes	27 (67,5 %)	3 (7,5 %)	10 (25 %)	40 (100 %)

Other triggers - mosquito bites (in two episodes), vaccination (in one episode)

done using Microsoft Excel computer program.

Results

Triggers

All of the 9 initial episodes of SSNS (100 %) and 18 out of 31 relapses (58.1 %) were triggered by acute, mostly afebrile viral upper respiratory tract infections. Only in 5 of these infections children were febrile. 2 out of 31 relapses (6.5 %) were triggered by mosquito bites and 1 (3.2 %) by vaccination (Table 2).

Average time to achieve remission

Average time to achieve remission with daily corticosteroid therapy in all 40 episodes of SSNS was 18, 3 +/- 14, 1 days. It was shorter in patients with Steroid-Dependent Nephrotic Syndrome (SDNS) compared to patients with non-SDNS (p=0,071) and shorter in small children with BSA < 1 m^2 compared to children with BSA > 1 m^2 (p = 0,058). The diffference did not reach statistical significance (Table 3).

The role of erythrocyte sedimentation rate in idiopathic SSNS in children

Average erythrocyte sedimentation rate (ESR) was 71,6 +/- 30,5 mm/h in initial episodes compared to 20, 5 +/- 23,8 mm/h in relapses (p = 0.000058). The difference in average ESR between patients with SDNS and those with non-SDNS as well as the difference between small children with BSA < 1 m^2 compared to children with BSA > 1 m^2 was not statistically significant (Table 4).

The correlation coefficient between time to achieve remission and ESR was 0,09 suggesting that ESR is not useful for predicting time of therapy needed to achieve remission (Figure 1).

The average concentration of C-Reactive Protein (CRP) in all patients was 12,0 +/- 52,5 mg/l (normal value in our laboratory is less than 8 mg/l). But without the extremely high value of CRP (327 mg/l) in a patient with peritonitis during one of the relapses, the average CRP was only 3,5 +/- 2,4 mg/l. The correlation coefficient between ESR and CRP was 0,39.

Discussion

Children with initial episodes of SSNS had much higher proportion of triggers of nephrotic syndrome compared to relapses. There has been no such an event in about one third of relapses. Most of the triggers were mild upper respiratory tract infections which are in concordance with data in literature [1]. The theory of immune system involvement in the pathogenesis of idiopathic nephrotic syndrome through dysfunction of various immune cells caused by viral infections is widely accepted [5]. However, it is worth mentioning that in this group of patients there were at least 10 acute infections and some other potential triggers (vaccinations and severe injuries, such as bone fractures) in the observation period that were not followed by a relapse. There were probably more such events but patients or their parents could not recall all of them at follow-up visits. This suggests that relapses in idiopathic nephrotic syndrome are often a consequence of other, intrinsic and unknown factors, and not necessarily triggered by environmental influences. Another study, analysing triggers of steroid-dependent and frequently relapsing nephrotic syndrome in children, showed that only 31 % of relapses were triggered by environmental influences, most often by a common cold (in 52 %), as compared to 68 % in the present study, with acute viral upper respiratory tract infection - common cold as the most common trigger as well (in 58 %). On the other hand, other relapses occurred with no such triggers but in 55 % occurred within 3 days prior to patient's follow-up visit suggesting the role of mental stress due to the patient's concern about visiting the hospital [6].

Table 3: Average time to achieve remission in different subgroups of children with idiopathic Steroid Sensitive Nephrotic Syndrome (SSNS) with level of statistical significance.

Subgroups of children with episodes of SSNS (n = 40)	Time to achieve remission (days, average +/- SD)	Level of statistical significance
Initial episodes (n = 9)	18,7 +/- 7,9	Not significant (p = 0,91)
Relapses (n = 31)	18,2 +/- 15,5	
SDNS (n = 25)	14,5 +/- 7,6	Not significant (p = 0,071)
Non – SDNS (n = 15)	24,7 +/- 6,8	
Children with BSA < 1 m² (n = 28)	14,8 +/- 9,8	Not significant (p = 0,058)
Children with BSA > 1 m² (n = 12)	26,7 +/- 18,9	

Abbreviations: SDNS: Steroid Dependent Nephrotic Syndrome; BSA: Body Surface Area; SD: Standard Deviation; n: number of nephrotic syndrome episodes.

Table 4: The role of Erythrocyte Sedimentation Rate (ESR) in idiopathic Steroid Sensitive Nephrotic Syndrome (SSNS) in children with level of statistical significance.

Subgroups of children with episodes of SSNS (n = 40)	Average ESR (mm/h, average +/- standard deviation)	Level of statistical significance
Initial episodes (n = 9)	71,6 +/- 30,5	**p = 0.000058**
Relapses (n = 31)	20,5 +/- 23,8	
SDNS (n = 25)	28,4 +/- 31,5	Not significant (p = 0,34)
Non – SDNS (n = 15)	39,2 +/- 36,3	
Children with BSA < 1 m² (n = 28)	34,1 +/- 36,6	Not significant (p = 0,62)
Children with BSA > 1 m² (n = 12)	28,3 +/- 24,9	

Abbreviations: SDNS: Steroid Dependent Nephrotic Syndrome; BSA: Body Surface Area; n: number of nephrotic syndrome episodes (initial episodes and relapses).

Additionally, retrograde analysis in one of the patients with SDNS revealed that symptoms of nasal congestion appeared after a relapse had begun. This suggests that nasal congestion may in fact be due to oedema of nasal mucosa rather than to upper respiratory tract infection as previously thought. But the lack of an environmental trigger in patients with SDNS is not a surprise since by definition these patients have a relapse due to the absence of corticosteroids rather than to an infectious trigger.

Average time to achieve remission with daily corticosteroid therapy was practically identical in initial episodes compared to relapses. It was shorter in patients with SDNS compared to patients with non-SDNS and shorter in small children with BSA < 1 m² compared to children with BSA > 1 m² but the diffference did not reach statistical significance. Comparison of steroid responsiveness in children according to BSA was included because mathematical models showed that weight-based dosing of corticosteroids may yield smaller values than BSA-based dosing in smaller children. This resulted in increased likelihood of frequently relapsing course of the disease in one study [7] but was not confirmed in this study.

Average ESR was significantly higher in initial episodes compared to relapses (p = 0.000058). The difference in average ESR between patients with SDNS compared to non-SDNS as well as the difference between small children with BSA < 1 m² compared to children with BSA > 1 m² was not statistically significant. The correlation coefficient between time to achieve remission and ESR was 0, 09. These results suggest that ESR is not a useful laboratory test for predicting time of therapy needed to achieve remission and consequently clinical course of disease in these patients, unlike in some rheumatic diseases. Since ESR is inflammatory marker it could potentially be influenced not only by a nephrotic syndrome but also by an infection triggering it. The average concentration of CRP in all patients was very low and there was no correlation between ESR and CRP. This is an expected finding since mild viral infections, that usually do not cause

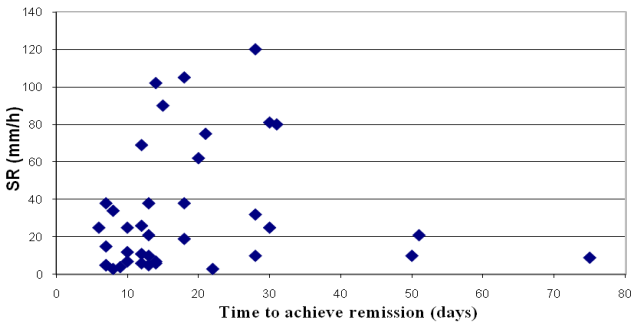

Figure 1: Correlation between time to achieve remission and Erythrocyte Sedimentation Rate (ESR).

significantly elevated CRP values, most often triggered a nephrotic syndrome episode. This suggests that ESR values in this study were not interfered with an infection, if present.

Study revealed that there was no correlation between histology result of renal biopsy and clinical course of SSNS in the presented sample. But the primary purpose of this study was not to analyze this association because of a small sample size which does not allow us to make these conclusions. However, it does suggest that the response to corticosteroids may be more predictive of further clinical course and prognosis than the histology result itself, a finding often observed in clinical practice. Similarly, a recent study in children showed that different variants of MCD, such as C1q or IgM nephropathy, do not predict a worse outcome compared to immune fluorescence-negative MCD [8].

Conclusion

Children with initial episodes of SSNS seem to have much higher proportion of triggers of nephrotic syndrome compared to relapses. Average time to achieve remission with daily corticosteroid therapy was very similar in initial episodes and relapses but shorter in patients

with SDNS and in small children with BSA < 1 m^2 (the diffference not statistically significant). Average ESR was significantly higher in initial episodes compared to relapses but there was no significant correlation between time to achieve remission and ESR. However, the results should be interpreted with caution given the relatively small sample size. On the other hand, the sample is for this reason perhaps more homogenous in terms of evaluation and treatment. Nevertheless, a study on bigger sample would be beneficial to further clarify some aspects of nephrotic syndrome in children that were evaluated in this paper.

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