

Original Research Article

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Triggering Factors for Relapses in Steroid Sensitive Nephrotic Syndrome

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ABSTRACT

Nephrotic syndrome (NS) is a chronic disorder in childhood Relapse occurs in more than two- thirds of children. Study the trigger factors of relapses in children with NS, and correlations with some demographic factors. A prospective study including 80 children with Steroid Sensitive NS, was carried out in the Pediatric Nephrology Clinic of Imamein Kadhman Medical City from November 2012 till end of May 2013. The following data were studied: Age, Gender, Age at diagnosis of NS, Number of days to get remission, Need for hospital admission. Triggering factors are grouped as: 1. Infections which is subdivided into: Acute respiratory Infections (ARI), Urinary Tract Infections (UTI), and others 2. Incomplait to treatment, 3. Stop treatment 4. Decrease dose. 5. Asthma attacks. 6. Change season. 7. No cause. Total number of 80 patients with NS with 228 relapses, which occurred more in males, male: female = 1.5: 1. Majority of patients were frequent relapsers 62(77.5%). Infections is the most common triggering factor (63.59%), followed by decreasing steroid dose (21.05%), stop treatment (6.14%), asthma attacks (4.82%), incomplait to treatment (2.63%). Respiratory infection was the main infection in male with 51 relapse (65.38%), P- value < 0.001, while UTI were more in females with 40 relapses (59.70%), with P- value <0.001. Infections, asthma attacks and decreasing dose are statically significant with male gender. Only asthma attacks which compromise 15.63% of hospital admission are statically significant with P- value 0.01. Infections are the most triggering factor for relapses in SSNS. Respiratory infection was more in males while UTI were more in females. Asthma attack correlated with hospital admission.

Keywords

Nephrotic Syndrome, relapses, triggers.

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Introduction

Nephrotic syndrome (NS) is a primarily a pediatric disorder and is 15 times more common in children than adults (Vogt *et al.*, 2007; Niaudet *et al.*, 2004).

The characteristic features are heavy proteinuria (>3.5gm /24hr in adults Or 40 mg/m2/hr in children), hypoalbuminemia (<2.5 g/dl), edema, and hyperlipidemia (Vogt *et al.*, 2007; Niaudet *et al.*, 2002).

Approximately 90% of children with NS have idiopathic nephrotic syndrome (INS) (Vogt *et al.*, 2007; Niaudet *et al.*, 2004; Feehally, 2000).

Idiopathic nephrotic syndrome includes 3 histological types: minimal change disease (MCD), mesangial proliferation, and focal segmental glomerulosclerosis (Vogt *et al.*, 2007; Niaudet *et al.*, 2004; Feehally, 2000; Bagga *et al.*, 2005).

Minimal change disease; the most common cause of INS in children, has a high relapse rate, with approximately half of patients developing steroid dependency.

There is a tendency for patient with MCD to run a relapsing-remitting course, approximately 30% of children experience only one attack and are definitively cured after single course of steroids. Relapse occurs in more than two-thirds of children and nearly 50% relapse more than 4 times per year (Feehally *et al.*, 2000).

Infection, viral or bacterial, can trigger relapses of INS and further complicate the course of the condition, prevention and treatment of which can reduce proteinuria without necessity of steroid (Moorani *et al.*, 2012)

An URTI or a febrile episode, asymptomatic UTI often precipitates a relapse, occasionally there is no obvious cause for relapse occurrence (Moorani *et al.*, 2012)

Despite the generally favorable prognosis in patients who respond to steroids. The original International Study of Kidney Disease in Children (ISKDC) reported a 60% rate of subsequent relapses, which can lead to complications, increased morbidity, and

decreased quality of life (Lombed *et al.*, 2013).

The main aim of this study is to study the trigger factors of relapses in children with nephrotic syndrome and to study some demographic factors in children with nephrotic syndrome and its relation with occurrence of relapses

Patients and methods

A prospective study including 80 children with Steroid Sensitive Nephrotic Syndrome (SSNS), was carried out in the Pediatric Nephrology Clinic of Imam Khomeini Medical City from November 2012 till end of May 2013.

A well constructed questionnaire was performed by the authors, and direct interview with the patients themselves or their parents, some of the information was taken from the files record as well.

Diagnosis of NS was made according to the following criteria: heavy proteinuria >40 mg/h/m² (for older children with collected 24hour urine); or protein/creatinine ratio >0.2 g/mmol, Albustix $\geq+++$ (for non-toilet-trained children or difficult collection of 24hour urine), hypo-albuminemia <2.5 g/dL, edema and hyperlipidemia.

Patients were grouped as 1.frequent relapsers: with ≥ 2 relapses within 6 months of the initial response or less than four relapses for any year thereafter 2. Infrequent relapsers : with < 2 relapses in 6 months of the initial response or less than four relapses for any year thereafter.

The following data were studied in these patients: Age, Gender, Age at diagnosis of NS, Number of days to get remission for each relapse, Need for admission in each relapse.

Triggering factors are grouped according to the causes into:

1. Infections which is subdivided into: respiratory, Urinary Tract Infections (UTI), and others 2. Incomplaint to treatment, 3. Stop treatment 4. Decrease dose. 5. Asthma attacks. 6. Change season. 7. No cause

The exclusions to this study are the following groups of patients: Patients less than one year of age, Steroid resistant cases, Secondary NS, Congenital NS.

Analysis of this prospective and follow up study performed with the statistical package for social science (SPSS) 19.0 and Microsoft excel 2010. Categorized data formulated as count and percentage. Chi- square test used to describe the association of these data. The level of statistical significant difference is below or equal to 0.05.

Results and Discussion

Total numbers of patients in this study were 80 patients who had 228 relapses during the study period.

Numbers of males were 48 (60%) while number of females were 32 (40%), Male: female ratio is 1.5: 1.

Age of patients at time of presentation was ranging between 1- 16 years, with the mean 7.47years \pm SD 3.53 years.

Age at time of diagnosis ranged between 8months and 14 years; with the mean age 4.32years \pm SD 2.84years.

Most children 41(51.25%) respond to steroid in < 1 week duration.

The majority of patients were frequent relapsers 62 (77.5%), while infrequent relapsers were 18 (22.5%).

Table 1 shows the triggering factors of 228 relapses of the patients. Infections are the most common triggering factor (63.59%), and the second triggers were the decreasing dose with 48 relapses (21.05%).

Regarding Infection; the respiratory infections constitute the most common type with 76 relapses (33.33%), followed by UTI with 61 relapses (26.75%)

Table 2 shows the relation of triggering factors for relapses with gender. Infections were the most common triggering factors in both sexes. Infections, asthma attacks and decreasing dose are statically significant with P value 0.006 for infection, 0.34 for asthma attacks and 0.048 for decreasing dose.

As shown in Table 3, the respiratory infections were the main infection in males with 51 relapse (65.38%), and is statically significant with P value < 0.001, while UTI made the most common infection in females with 40 relapses (59.70%), and is statically significant with P- value <0.001.

Table 4 shows the relation between the triggering factors and the mean patient's age, the results show that the age is not statically significant in relation to triggering factors.

Table 5 shows the relation of triggering factors with time for response to steroid therapy. It shows that majority of relapses caused by infections (76%) responded to steroid in 1- 2 weeks with statically significant with P- value 0.03.

Table 6 shows the comparison between the triggering factors with frequent and infrequent relapsers, it shows that only incompliant to treatment in regarding to infrequent relapses was statically significant with P- value 0.016.

Table 7 shows the relation between the triggering factors and need for admission, we see that 56.25% of relapses that need admission were triggered by infections although it is statically not significant with P- value > 0.05. Only asthma attacks which compromise 15.63% of total admission to hospitals are statically significant with P-value 0.01.

In other medical references and books there is similar result of male predominance with male: female ratio ranging from 4:1 - 1.3:1 (Moorani, 2012; Senguttuvan *et al.*, 2004; Constantinescu *et al.*, 2000; Ali *et al.*, 2008; Rahi *et al.*, 2009)

The age range of patients at presentation in this study was similar to many studies (Moorani, 2012; Constantinescu *et al.*, 2000; Ali *et al.*, 2008; Rahi *et al.*, 2009).

Mean age at presentation with lower figures was reported in studies from Iran, Japan, New Jersey, Bangladesh (Constantinescu *et al.*, 2000). These differences might reflect their medical health system that the patients continue treatment and follow up from the time of diagnosis in the same hospital rather than referral.

In a study done in Karachi /Pakistan, among 720 children with SSNS; mean age at initial diagnosis and presentation was 5.4 ± 2.7 years and 7.99 ± 3.12 years respectively (Moorani, 2011), which is similar to our results in that there is a gap between the age of diagnosis and the age of presentation. This is explained that ImameinKadhimein Medical City is a tertiary center and patients have been seen by different medical centers before referral. International study of kidney disease in children reported that response to steroid occur in most cases within 10-15days (median 11 days). Which is nearly similar to results of this study. Two studies reported less percentage of response to

steroid below one week (Bircan *et al.*, 2002), this differs from our study and the cause may be due to differences in the study sample.

Patients took an average of 13.9 ± 1.6 days to achieve remission, ranging from 2 to 60 days in Alexandru *et al.*, study (2000). He detected no correlation between the age of patients and the number of days to remission

A study from Korea found that the days from initial attack to remission was longer in children with frequent relapses (12.9 ± 0.5 vs. 16.2 ± 1.1 , P value <0.05).

Different studies from different regions indicated the predominance of frequent relapsers ranging from 50.97% - 83%.

While two studies from Iran and Korea found less frequent relapsers in 34% and 39.7% respectively. This difference because these studies included non relapsers in their analysis.

Sarker *et al.*, study showed that children below 5 years are more likely to be frequent relapsers (68%), compared to those above 5 with P value of 0.019. Sex was not found to be associated with frequency of relapses.

Overall infections as triggering for relapses was detected as 62.88% by Moranni study (2011) which are nearly similar to this study.

Results of this study came in agreement with others, which indicated that Respiratory infections were the commonest triggering factor for relapses in percentages of 46.6% - 65.9%.

In a previous Iraqi study, URTI versus Pneumonia were found as triggering for 38 versus 8 relapses out of 120 relapses (Rahi *et al.*, 2009). It is obvious that viral URTI are the commonest respiratory infections.

In a Pakistan study poor compliance occurs in 47 relapses (10.44%), which are higher than our figures. This might be related to the study place, as our patients were more adherent to clinical visits and treatment in the tertiary center. In Japan study, relapses without triggering factors was reported in

68.6%. This big difference reflected the different environmental factors between the two different populations.

UTI constituted a second rank for triggering in 25% of relapses in Pakistani study which is nearly similar to ours

Table.1 Triggering factors of 228 relapses in children with Steroid Sensitive Nephrotic Syndrome

| Triggering factors | | Number of relapses | % |
|--------------------|---------------------------------|--------------------|--------------|
| 1 | Infection | 145 | 63.59 |
| | A. Respiratory | 76 | 33.33 |
| | i URTI | 52 | 22.81 |
| | ii Tonsillitis | 13 | 5.70 |
| | iii Pneumonia | 11 | 4.82 |
| | B. UTI | 61 | 26.75 |
| | C. Other infections | 8 | 3.50 |
| | i Skin infection | 3 | 1.32 |
| | ii Hepatitis | 2 | 0.88 |
| | iii GE | 2 | 0.88 |
| | iv Mouth ulcers | 1 | 0.44 |
| 2 | Incompliant to treatment | 6 | 2.63 |
| 3 | Stop treatment | 14 | 6.14 |
| 4 | Decrease dose | 48 | 21.05 |
| 5 | Asthma attacks | 11 | 4.82 |
| 6 | Change season | 2 | 0.88 |
| 7 | No cause | 2 | 0.88 |
| | Total | 228 | 100 |

Table.2 Relation between triggering factors for relapses and gender in children with steroid sensitive nephrotic syndrome

| Cause | Male | | Female | | Total | | P value |
|--------------------------|------------|-------------|-----------|-------------|------------|------------|---------------|
| | No. | % | No. | % | No. | % | |
| Infection | 78 | 56.52% | 67 | 74.44% | 145 | 63.6 | 0.006* |
| incompliant to treatment | 4 | 2.90% | 2 | 2.22% | 6 | 2.63 | 0.755 |
| Stop treatment | 9 | 6.52% | 5 | 5.56% | 14 | 6.14 | 0.766 |
| Decrease dose | 35 | 25.36% | 13 | 14.44% | 48 | 21.05 | 0.048* |
| Asthma attack | 10 | 7.25% | 1 | 1.11% | 11 | 4.82 | 0.034* |
| Change season | 0 | 0.00% | 2 | 2.22% | 2 | 0.88 | 0.078 |
| No cause | 2 | 1.45% | 0 | 0.00% | 2 | 0.88 | 0.251 |
| Total | 138 | 100% | 90 | 100% | 228 | 100 | |

Table.3 Relation between subdivisions of infections as triggering factors for relapses and gender

| Infections | Male | % | female | % | Total | P- value |
|-------------|------|--------|--------|--------|-------|-------------------|
| Respiratory | 51 | 65.38 | 25 | 37.31 | 76 | 0.001*< |
| UTI | 21 | 26.92 | 40 | 59.70 | 61 | 0.001*< |
| Others | 6 | 7.69 | 2 | 2.99 | 8 | 0.215 |
| Total | 78 | 100.00 | 67 | 100.00 | 145 | |

Table.4 Relation between triggering factors and the mean age group of occurrence of relapses in children with steroid sensitive nephrotic syndrome

| Cause | N | Mean men age | SD | P |
|--------------------------|-----|--------------|------|-------|
| Infection | 145 | 7.21 | 3.23 | 0.319 |
| incompliant to treatment | 6 | 9.67 | 2.34 | |
| stop treatment | 14 | 8.04 | 3.96 | |
| decrease dose | 48 | 6.91 | 3.62 | |
| asthma attack | 11 | 6.61 | 2.24 | |
| change season | 2 | 8.50 | 4.95 | |
| no cause | 2 | 10.50 | 3.54 | |
| Total | 228 | 7.28 | 3.33 | |

Table.5 Relation between the triggering factors for 228 relapses and time of remission

| Cause' | Time of remission (in weeks) | | | | | | | | P |
|---------------------------------|------------------------------|--------|-------|--------|------|--------|-------|--------|---------------|
| | <1 w | % | 1-2 w | % | >2 w | % | Total | % | |
| Infection | 61 | 57.01% | 54 | 76.06% | 30 | 60.00% | 145 | 63.60% | 0.030* |
| Incompliant to treatment | 6 | 5.61% | 0 | 0.00% | 0 | 0.00% | 6 | 2.63% | --- |
| Stop treatment | 9 | 8.41% | 4 | 5.63% | 1 | 2.00% | 14 | 6.14% | --- |
| Decrease dose | 24 | 22.43% | 10 | 14.08% | 14 | 28.00% | 48 | 21.05% | 0.161 |
| Asthma attacks | 6 | 5.61% | 1 | 1.41% | 4 | 8.00% | 11 | 4.82% | --- |
| Change season | 1 | 0.93% | 0 | 0.00% | 1 | 2.00% | 2 | 0.88% | --- |
| No cause | 0 | 0.00% | 2 | 2.82% | 0 | 0.00% | 2 | 0.88% | --- |
| Total | 107 | 100% | 71 | 100% | 50 | 100% | 228 | 100% | --- |

Table.6 Relation between triggering factors and frequency of relapses

| Cause | Infrequent relapse | | Frequent relapse | | Total | | P value |
|--------------------------|--------------------|--------|------------------|--------|-------|--------|--------------|
| | No. | % | No. | % | No. | % | |
| Infection | 12 | 66.67% | 133 | 63.33% | 145 | 63.60 | 0.777 |
| Incompliant to treatment | 2 | 11.11% | 4 | 1.90% | 6 | 2.63 | 0.016 |
| Stop treatment | 2 | 11.11% | 12 | 5.71% | 14 | 6.14 | 0.359 |
| Decrease dose | 1 | 5.56% | 47 | 22.38% | 48 | 21.05 | 0.092 |
| Asthma attack | 1 | 5.56% | 10 | 4.76% | 11 | 4.82 | 0.879 |
| Change season | 0 | 0.00 | 2 | 0.95% | 2 | 0.88 | 0.677 |
| No cause | 0 | 0.00 | 2 | 0.95% | 2 | 0.88 | 0.677 |
| Total | 18 | 100.0% | 210 | 100.0% | 228 | 100.00 | |

Table.7 Relation between triggering factors in 228 relapses and the need for admission

| Triggering factors | (need for admission) | | | | Total | P |
|---------------------------------|-----------------------|---------|-----|---------|-------|--------|
| | No | % | Yes | % | | |
| Infection | 127 | 64.80% | 18 | 56.25% | 145 | 0.352 |
| Incompliant to treatment | 5 | 2.55% | 1 | 3.13% | 6 | 1 |
| Stop treatment | 11 | 5.61% | 3 | 9.38% | 14 | 0.423 |
| Decrease dose | 43 | 21.94% | 5 | 15.63% | 48 | 0.491 |
| Asthma attacks | 6 | 3.06% | 5 | 15.63% | 11 | 0.010* |
| Change season | 2 | 1.02% | 0 | 0.00% | 2 | 1 |
| No cause | 2 | 1.02% | 0 | 0.00% | 2 | 1 |
| Total | 196 | 100.00% | 32 | 100.00% | 228 | |

In Sarker study, data show that the FRNS group had a significantly higher incidence of UTI and RTI compared to the IFRNS 44% vs 24% for UTI and 34% vs 16% for RTI. The total frequency of infection was observed to be almost double in the former group (72%) compared to latter group (38%) (Sarker *et al.*, 2012)

An Indian study reported that incidence of UTI in boys was 71 /320 (22.4%) as against 49/203 (24.1%) in girls. While for Acute respiratory infection; 23 (7.1%) occurred in males compared to 12 (5.9%) in females (8). These results are similar to our conclusions. It is well known that female gender is risk factor for UTI (Vogt *et al.*, 2007; Niaudet *et al.*, 2002)

Asthma was the trigger for relapses in 12 out of 77 children with NS in UK study. In this study asthma triggering 4.82% of relapses and significantly more in males. Asthma is common problem and mostly asthmatic attack is aggravated with URTI which might underestimate the asthma itself as a trigger factor. This study shows that all age groups are affected equally by different triggers. This may be related to the wide range of age group for NS occurrence and the nature that 70% of NS continue relapsing.

From children with SSNS who respond to steroid treatment within 1-2 weeks, (76.6%) were triggered by infections which is higher than those responding less than 1 week (57.01%) ;result was statically significant with P-value = 0.030. It was stated that response occurs in most cases within 10-15 days (median 11 days).

Incompliant to treatment was found to be significantly correlated with triggering relapses in the IR group. This reflects that adherence to treatment regimen will affect the disease in this group. However, we see

that infections are the commonest triggering factors in both frequent and infrequent relapses nephrotic syndrome although not showing significant results.

Significant admission occurs in relapses that triggered by asthma attacks. This reflects the severity of the relapses and the need for hospital management as most asthma attacks are aggravated by URTI.

Several studies detected that most of admission are due to relapses triggered by infections. This indicated the difficulty in achieving remission with outpatient management need for hospital treatments in these relapses.

In conclusion, infections are the most triggering factor for relapses in SSNS. Respiratory infection as triggering factors was significantly correlated with males while UTI were significantly correlated with females. Infections, decrease dose of steroid and asthma attacks had significant correlation with male gender. Majority of relapses caused by infection, responded to steroid in 1- 2 weeks. Incompliant to treatment correlates significantly with relapses in IR group. Asthma attack is the only trigger that is statically significant as a cause of hospital admission.

A good search for source of infection with relapses is indicated for treatment particularly ARI and UTI.

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