Increased behavioural problems associated with corticosteroid use in children with nephrotic syndrome: a Southeast Asian perspective

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Abstract

Introduction: The study was performed to determine the psychological problems in children with idiopathic nephrotic syndrome (INS) while they were on steroid therapy, as compared to healthy children.

Methods: This prospective cohort study was conducted in a paediatric clinic of a tertiary hospital. Parents of the participants in the INS group and control group (comprising children without chronic illness) completed questionnaires using the Child Behavioural Checklist (CBCL). The CBCL measures a range of age-specific emotional and psychological problems, including internalising and externalising domains. Analyses of the CBCL scores between groups were done using Mann–Whitney U test.

Results: A total of 140 children were recruited with an equal number in the INS and control groups. There was a significant difference in the mean total CBCL scores between the INS group and the control group, specifically in the withdrawal, somatic, anxious and aggressiveness subdomains. Similar findings were demonstrated in correlation between total psychological problems and corticosteroid dosage. In the INS group, steroid dose and cushingoid features were found to have a significant positive association with internalising psychological problems.

Conclusion: Children with INS on corticosteroid treatment showed an increase in internalising and externalising scores, as compared to healthy children.

Keywords: Corticosteroid, externalising, internalising, nephrotic syndrome, psychology

INTRODUCTION

Childhood nephrotic syndrome is a clinical syndrome characterised by nephrotic-range proteinuria (>$40$ mg/m²/h or >$1$ g/m²/day), early morning albumin to creatinine ratio of >$2$ mg/mg with a low serum albumin level (<$25$ g/L) and generalised oedema. [1] The annual incidence rate of childhood nephrotic syndrome is $2–7$ cases per 100,000 children aged <$16$ years (both internationally and locally). [2] Nephrotic syndrome has many aetiologies, including primary causes (or idiopathic nephrotic syndrome [INS]) such as minimal change disease (MCD), focal segmental glomerulosclerosis and membranous glomerulonephritis, and secondary causes such as systemic lupus erythematosus. Idiopathic nephrotic syndrome is the most common form of childhood-onset nephrotic syndrome, affecting more than $90\%$ of children aged $1–10$ years and $50\%$ of those aged >$10$ years. [3] Eighty percent of cases with childhood-onset INS suffer from MCD. [4–6] Steroid-sensitive nephrotic syndrome is a relatively benign disease with a good prognosis. [7] It has been demonstrated that treatment of childhood-onset nephrotic syndrome with corticosteroids is associated with increased incidence of psychosocial problems. [8–10] This negative effect is most pronounced in the early stages of treatment. [11–13] This study was performed to determine the psychological problems in children with INS while they were on steroid therapy, as compared to healthy children.
nephrotic syndrome with corticosteroids (a class of steroid hormones) significantly reduces the morbidity and mortality rates.[9] Corticosteroids are naturally occurring or artificially produced; synthetic corticosteroids mimic the actions of naturally occurring ones. Examples of synthetic corticosteroids include betamethasone, prednisolone, methylprednisolone and dexamethasone. In the paediatric population, corticosteroids are frequently used to treat conditions such as asthma, malignancy, inflammatory bowel disease and rheumatoid arthritis.

Steroid-induced toxicities such as stunted growth, hypertension, obesity and cataracts have been described by many studies worldwide. The effects of steroid therapy on emotional disturbances such as anxiety have also been well acknowledged. Corticosteroids affect behaviour via indirect mechanisms. They have been shown to induce chemical changes in specific sets of neurons responsible for influencing behavioural outcomes by either strengthening or weakening particular neural pathways. At low circulating levels, corticosteroids exert permissive action on the mediation of acute freezing behaviour and acute fear-related plus maze behaviour via the brain mineralocorticoid receptor mechanism. In contrast, at high levels, corticosteroids enhance the acquisition, conditioning and consolidation of an inescapable stressful experience via their glucocorticoid receptor mechanism.[9]

Hall et al.[10] examined the effect of corticosteroids on the behaviour of children with nephrotic syndrome from May 1999 to November 2000. They concluded that children with nephrotic syndrome who are on high-dose oral steroids are at risk of developing behavioural changes. In a cohort study, Soliday et al.[11] demonstrated behavioural changes among children with INS during periods of relapse, which included anxiety, depression and aggressiveness. Other studies on the behavioural effect of corticosteroids on children with INS were conducted by Manti et al.[12] and Youssef et al.[13] They reported that children with INS presented with internalising problems, including withdrawal and somatic complaints, but not anxiety, depression or externalising problems. However, when the children were on high-dose steroid therapy, their anxiety, depression and aggressiveness scores increased significantly. It is apparent that children with INS who are on steroid therapy are at high risk of developing psychological problems. Studies looking into psychological problems among children with INS who are on steroid therapy are limited in Southeast Asian countries.

This study aimed to examine psychological problems in children with INS when they were on corticosteroid therapy. Specifically, we tried to determine if there is an increase in specific emotional and behavioural problems in children with INS compared to healthy children, and identify the association between psychological problems and selected sociodemographic and clinical variables.

METHODS

This prospective cohort study was conducted between January 2019 and September 2019 at a tertiary hospital where all paediatric nephrology cases from the northeast coast of Malaysia are referred to. Ethical approval was obtained from the Human Research Ethics Committee of Universiti Sains Malaysia (USM/JEPM/18020117).

Participants of the study were children aged 6–18 years who had INS and were receiving steroid therapy at the paediatric nephrology clinic. Children diagnosed with infantile, secondary nephrotic syndrome or steroid-resistant nephrotic syndrome were excluded. The control group consisted of comparable, age-matched healthy children with no known chronic medical illness, who were recruited from the general paediatric ward.

Following informed consent, the parents of the participants were given a set of questionnaires, which included a Bahasa Malaysia-validated version of the Child Behavioural Checklist (CBCL) for those aged 6–18 years and a sociodemographic checklist.[14] The CBCL is a 113-item parent-reported questionnaire that measures the range of emotional and psychological problems in children aged 6–18 years on a three-point Likert scale. The six scales of interest used in this study were the Internalising Domain, Externalising Domain, Withdrawn/Depressed, Somatic Complaints, Anxious/Depressed and Aggressive Behaviour scales. The Total Problem summarises the six scales. The Internalising Domain scale combines the scores obtained from emotional problems subscales such as Withdrawn/Depressed, Anxious/Depressed and Somatic Complaints. The Externalising Domain scale assesses for a combination of behavioural problems subscales, which include Aggressive Behaviour and Delinquent behaviour. The Total Problems scale combines the scores from the Internalising and Externalising Domain scales.

The inter-interviewer and test–retest reliabilities of the CBCL scores were supported by the inter-class correlation of 0.93–1.00 for the mean item scores obtained by different interviewers and for reports by parents on two occasions 7 days apart.[14] The internal consistency of the competence scales was supported by alpha coefficients of 0.63–0.79 on the CBCL scales. The criterion-related validity of the CBCL scales was supported by multiple regressions, odds ratios and discriminant analyses, all of which showed significant ($P < 0.01$) discrimination between the children who were referred and the children who were not referred.[15,16]

Sociodemographic information, which includes the children’s age, gender, race, level of education and monthly family income, was compiled by a research assistant. We also recorded clinical characteristics such as the children’s age at INS diagnosis, duration of illness, current dosage of steroid, duration of treatment, and medical complications such as hypertension, cataract, cushingoid features and stunted growth.
The scores for psychological problems (total CBCL scores, and internalising and externalising problems) were compared between children with INS who were on corticosteroid therapy and healthy children using the Mann–Whitney U test. Next, the score for psychological problems among children with INS was correlated with selected variables, including sociodemographic and clinical characteristics, using the Spearman correlation test. A sample size of 70 children per group was required to achieve a power of 80% and a statistical significance of 0.05, with the possibility of a 10% dropout rate.

**RESULTS**

A total of 140 children aged 6–18 years were recruited in this study: 70 children with INS and 70 healthy children. Their sociodemographic and clinical characteristics data are presented in Table 1. The majority of the children were male and Malay, with a mean age of 10 (INS group: 10.09 ± 2.90; control group: 10.54 ± 3.63) years. Most of the children were in primary school at the time of the study and belonged to a low socioeconomic background. The mean corticosteroid dosage in the INS group was 22.50 ± 19.41 mg, with a mean duration usage of 31.07 ± 27.19 weeks. The most common medical complications reported in children with INS were hypertension, followed by cataract, cushingoid features and stunted growth [Table 2].

There was a significant difference in the mean total score for psychological problems between the INS and control groups, as reflected in the CBCL scores and subscores. Children with INS had higher median scores (total score and scores across the six subdomains), as presented in Table 3. Table 4 shows the relationship between corticosteroid dosage and duration of use with psychological problems in children with INS. Except for externalising problems and aggressiveness, there was a significant positive correlation between corticosteroid dosage and most of the psychological problems. However, no significant correlation was found between all subscales of psychological problems and treatment duration, except for anxiety.

There were significant linear positive associations between cushingoid features and dose with internalising psychological problems when adjusted for other variables, as demonstrated in Table 5. Patients with cushingoid features had a 13.50-unit

### Table 1. Demographic information of the INS and control groups (N=140).

| Demographic     | n (%)      | P*  |
|-----------------|------------|-----|
| **Gender**      |            |     |
| Male            | 43 (61.4)  | 0.392 |
| Female          | 27 (38.6)  |     |
| **Race**        |            |     |
| Malay           | 70 (100)   | 0.496 |
| Others*         | 2 (2.9)    |     |
| **Family income** (RM) |   | 0.757 |
| <3,000.00       | 49 (70)    |     |
| ≥3,000.00       | 21 (30)    |     |
| **Education level** |   |     |
| Primary         | 53 (75.7)  | 0.249 |
| Secondary       | 17 (24.3)  |     |
| **Others**      |            |     |

*Others refer to one Siamese and one Chinese. 1RM 1=USD 0.24. *Chi-square test. INS: idiopathic nephrotic syndrome

### Table 2. Clinical characteristics of children with idiopathic nephrotic syndrome (n=70).

| Characteristic          | Mean±SD     |
|-------------------------|-------------|
| Age at diagnosis (yr)   | 5.77±8.66   |
| Duration of illness (mth)| 51.60±75.54|
| Current dosage of steroid (mg) | 22.50±19.41|
| Duration of steroid (wk) | 31.07±27.19|
| Medical complications*  |             |
| Hypertension            | 25 (35.7)   |
| Cataract                | 9 (12.9)    |
| Cushingoid              | 9 (12.9)    |
| Stunted growth          | 2 (2.9)     |

*Data presented as n (%). SD: standard deviation

### Table 3. Total CBCL, major domains and subscale scores of the INS and control groups (N = 140).

| Variable      | Median (IQR) | P*  |
|---------------|--------------|-----|
| Total score   | 26.0 (31.50) | 13.0 (25.50) | <0.001 |
| Internalising | 7.5 (10.3)   | 2.0 (5.5)   | <0.001 |
| Externalising | 10.0 (9.3)   | 3.0 (9.0)   | <0.001 |
| Withdrawal    | 2.0 (3.0)    | 0.0 (2.0)   | 0.020 |
| Somatic       | 4.0 (5.0)    | 1.0 (3.0)   | <0.001 |
| Anxious       | 2.0 (5.25)   | 1.0 (2.0)   | 0.038 |
| Aggressiveness| 8.0 (7.5)    | 3.0 (7.0)   | <0.001 |

*Mann–Whitney U test. CBCL: Child Behavioral Checklist. INS: idiopathic nephrotic syndrome, IQR: interquartile range

### Table 4. Correlation between duration and dosage of steroids and psychological problems in children with INS (n=70).

| Psychological problem | Duration | Dosage | P*  |
|-----------------------|----------|--------|-----|
| Internalising         | 0.20     | 0.43†  |
| Externalising         | 0.07     | 0.17†  |
| Withdrawal            | 0.09     | 0.50†  |
| Somatic               | 0.13     | 0.27†  |
| Anxious               | 0.25†    | 0.44†  |
| Aggressive            | 0.00     | 0.14†  |

*Spearman correlation coefficient. †P<0.01. ‡P<0.05. INS: idiopathic nephrotic syndrome
higher internalising total score (adjusted $b$ 13.50, 95% confidence interval [CI] 7.99, 19.00). Every increment in dose by 1 unit would increase the internalising score by 0.13 unit (adjusted $b$ 0.13, 95% CI 0.03, 0.22).

Multiple linear regression shows a significant positive linear relationship between cushingoid features and externalising psychological problems [Table 5]. Every patient with cushingoid features would increase the externalising score by 6.58 (adjusted $b$ 6.58, 95% CI 1.90, 11.25). On the contrary, every increment of age by 1 year would decrease the externalising score by 0.64 (adjusted $b$ −0.64, 95% CI −1.18, −0.10).

**DISCUSSION**

Although psychological problems in children who receive corticosteroids have been acknowledged, there are limited studies on children with INS in Asia. The present study, which was conducted in a Southeast Asian country, demonstrated consistent findings. Cushingoid features and higher corticosteroid dosage were found to influence internalising psychological problems. In contrast, externalising psychological problems were associated with increased age and cushingoid features.

We chose the CBCL to explore psychological problems, as it is a widely used instrument with one of the best validated questionnaires. The CBCL had an excellent reproducibility and cross-cultural generalisability when it was applied in more than 60,000 healthy subjects in more than 30 countries.\(^{[17,18]}\)

The results showed significantly more psychological problems among children who received corticosteroid therapy compared to healthy children. Most of the psychological subscales, such as internalising, externalising, withdrawal, somatic, anxious and aggressiveness, had significant $P$ values ($<0.05$). The results from this study were compared to those of another study performed on children receiving corticosteroid therapy for asthma and malignancy, which demonstrated disturbance in behaviour, specifically depression, anxiety, restlessness and withdrawal.\(^{[19-21]}\) These findings are similar to the results of other studies. This might be due to the high dosage and long treatment duration or usage, particularly in chronic illnesses such as nephrotic syndrome and cancer.

The use of high-dose steroids strongly correlated with internalising problems whereby the children are withdrawn and anxious and manifest somatic syndrome. This finding
Cushing's syndrome may be connected with psychological problems, and it has been proposed that children with nephrotic syndrome might be susceptible to the side effects of corticosteroids because of the amplified free serum prednisolone concentrations. It was difficult to differentiate between the effect of treatment and that of chronic diseases on behavioural problems. The negative influence of chronic illnesses on psychological growth is well accepted, and epidemiological studies have projected that children with chronic diseases are 2.0–2.4 times more likely to develop psychological and behavioural problems. These problems might correlate better with the duration of illness than with the duration of corticosteroid therapy. The lengthy duration of medication use, repeated contact with the medical staff, disruption in schooling and daily activities, and anxiety among parents about the illness may contribute to the increase in anxiety and depression among children.

The present study also demonstrated a significant association between cushingoid features and corticosteroid therapy with internalising psychological problems. Cushingoid features also had a positive association with age on externalising psychological problems. The aetiological mechanism by which corticosteroids affect behaviour is multifactorial. Corticosteroid receptors are situated closely throughout the hippocampus and amygdala, regions of the brain that are believed to be intimately involved in behaviour, mood and memory. Cushing's syndrome may be connected with reduced hippocampal volume, as demonstrated by magnetic resonance imaging. It has been proposed that children with nephrotic syndrome might be susceptible to the side effects of steroids because of the amplified free serum prednisolone levels measured during episodes of hypoalbuminaemia.

Optimising steroid therapy in children with INS can be challenging due to the potential psychological side effects during treatment. Parents need to be well informed and made aware of the potential psychological consequences for their children, especially during the initial phase of steroid therapy. Otherwise, alternative steroid-sparing therapy can be considered.

The main limitation of the current study is that our findings cannot be extrapolated to children younger than 6 years old because the version of CBCL that we used in the study is applicable only to children aged 6–18 years.

In conclusion, children who received corticosteroid therapy for INS often experienced significant psychological problems. Parents should be alerted in advance about the potential magnitude of these side effects to be better prepared for behavioural problems when their child is on high-dose corticosteroids. Proactive measures, such as psychological and stress management support, should be readily available at the treatment centres.

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**Conflicts of interest**

There are no conflicts of interest.

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