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Increased internalising and externalising behavioural problems associated with corticosteroid usage in children with nephrotic syndrome: a South East Asian perspective

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ABSTRACT

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

Methods: It was a prospective cohort study conducted in a paediatric clinic of a tertiary hospital. Parents of participants, both in the INS group and the control group comprising children without chronic illness, were asked to complete questionnaires using the Child Behavioral Checklist (CBCL). 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 INS group children and control group children, specifically in the withdrawal, somatic, anxious, and aggressiveness sub-domains. Similar findings were demonstrated in a correlation between total psychological problems with the dosage of corticosteroid. Within the INS children, 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 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/d), early morning albumin to creatinine ratio of >2 mg/mg with a low serum albumin level (<25g/L), and generalised oedema.[1] The annual incidence rate of the syndrome is two to seven cases per 100,000 children younger than 16 years—both internationally and locally.[2] Nephrotic syndrome has many aetiologies, which include 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. INS is the most common form of childhood-onset nephrotic syndrome, affecting more than 90% of children aged 1–10 years and 50% of those older than 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] Corticosteroids are steroid hormones that can be both naturally and artificially produced. Synthetic corticosteroids mimic the actions of naturally occurring ones. In the paediatric population, corticosteroids are frequently used to treat conditions such as asthma, malignancy, inflammatory bowel disease and rheumatoid arthritis. Examples of synthetic corticosteroids include betamethasone, prednisolone, methylprednisolone and dexamethasone. It has been demonstrated that the use of corticosteroids in the treatment of childhood-onset nephrotic syndrome significantly reduces the morbidity and mortality rate.[8] 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 been acknowledged. Corticosteroids exert their effect on behaviour via indirect mechanisms. They have been shown to induce chemical changes in specific sets of neurons responsible for influencing behavioural outcomes in the form of 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, they 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 regarding the behavioural effect of corticosteroids on children with INS was 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 they 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 at examining 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 to identify the association between psychological problems and selected sociodemographic and clinical variables.

METHODS

This prospective cohort study was conducted between January 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/JEPeM/18020117).

Participants were parents of children with INS, aged 6–18 years, who were receiving steroid therapy at a paediatric nephrology clinic. Children diagnosed with infantile, secondary nephrotic syndrome or steroid-resistant nephrotic syndrome were excluded. Comparable, age-matched, healthy children with no known chronic medical illness were recruited from the general paediatric ward to serve as the control group.

Following informed consent, the participants were given a set of questionnaires, which included a Bahasa-Malaysia–validated version of the Child Behavior Checklist (CBCL) for those aged 6–18 years and a socio-demographic checklist.[14] 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 3-point Likert scale. The six scales of interest used in this study are the Internalising Domain, Externalising Domain, Withdrawn/Depressed, Somatic Complaints, Anxious/Depressed, Aggressive Behaviour and Total Problems scales. The Internalising Domain scale combines the scores obtained from emotional problems sub-scales such as Withdrawn/Depressed, Anxious/Depressed and Somatic Complaints. The Externalising Domain scale assesses for a combination of behavioural problems sub-scales, 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 children who were referred and children not referred.[15,16]

Socio-demographic information was compiled by a research assistant who recorded the children's age, gender, race, level of education and monthly family income. In addition, clinical characteristics information including children's age at INS diagnosis, duration of illness, current dosage of steroid, duration of treatment, as well as medical complications including hypertension, cataract, cushingoid features and stunted growth were also recorded.

The scores for psychological problems were compared between children with INS who were on corticosteroid therapy and healthy children using the Mann–Whitney U test. Psychological problems refer to the total CBCL scores, internalising problems and externalising problems.

Next, the score for psychological problems among children with INS was correlated with selected variables, including socio-demographic 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 parents of children aged 6–18 years were recruited in this study: 70 children with INS and 70 healthy children. Their socio-demographic and clinical characteristics data are presented in Table 1. The majority of the children were male and Malay by race, with a mean age of 10 years (INS group: mean ± standard deviation [SD] = 10.09 ± 2.90; control group: mean ± SD = 10.54 ± 3.63). Most of the children were in primary school at the time of the

study and belonged to a low socio-economic background. The clinical characteristics data demonstrated that the mean corticosteroid dosage consumed by children with INS was 22.50 ± 19.41 mg, with a mean usage duration 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 patient and control groups, as reflected in the CBCL scores and sub-scores. Children with INS had a higher median total CBCL score and all six sub-domains, as presented in Table 3.

Table 4 demonstrates a significant positive correlation between corticosteroid dosage and most psychological problems in children with INS, except for externalising and aggressiveness. However, no significant correlation was found between all sub-scales 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 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 in Table 6 shows a significant positive linear relationship between cushingoid features and externalising psychological problems. 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, studies among children with INS in the Asian region are limited. The present study demonstrated consistent findings when it was conducted in one of the Southeast Asian countries. 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 CBCL to explore psychological problems because it is widely used and one of the best-validated questionnaires. 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 sub-scales—such as internalising, externalising, withdrawal, somatic, anxious and aggressiveness—had significant p values (<0.05). The results from this study were compared with 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 were similar to the results of other studies. This might be due to high-dose corticosteroid therapy with a long treatment duration or usage, particularly in chronic illnesses such as nephrotic syndrome and cancer.

The high-dose steroids strongly correlated with internalising problems where the children are withdrawn and anxious and manifest somatic syndrome. This finding was consistent with two previous studies conducted by Soliday et al[11] and Hall et al, with smaller sample sizes.[10] The study demonstrated that most of the behavioural disturbances occurred at a higher prednisolone dosage administered (1 mg/kg every 48 h or more), and their regression

analysis showed that steroid dosage was a strong predictor of abnormal behaviour. A study by Mishra et al[22] showed that strong relationships were observed for internalising ($r > 0.65$, $p < 0.001$), externalising ($r > 0.68$, $p < 0.001$) and total ($r > 0.81$, $p < 0.001$) scores with cumulative dose of steroids.

However, there were no significant correlations between psychological problems and corticosteroid therapy duration in our study. This finding was in line with other studies conducted on the adult population, where the results showed that corticosteroid therapy duration had no effect on psychological problems.[23-25] It was quite 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 was well accepted, and epidemiological studies have projected that children with chronic diseases were 2.0–2.4 times more likely to cultivate psychological and behavioural problems.[26] These problems might correlate better with the duration of illness than with duration of corticosteroid therapy. The lengthy period required to take medication, repeated contact with 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.[12]

The present study also demonstrated a significant association between cushingoid features and corticosteroid therapy used 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, which are regions of the brain that are believed to be intimately involved in behaviour, mood and memory.[27] Cushing's syndrome may be connected with reduced hippocampal volume, as demonstrated by magnetic resonance imaging.[28] 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.[29,30]

Optimising steroid therapy in children with INS can be challenging, as we acknowledge 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.[11] Otherwise, alternative steroid-sparing therapy can be considered.

This study has some limitations whereby the findings cannot be extrapolated to children younger than 6 years because the version of CBCL used is applicable only to those aged 6 years and older.

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 allow better preparations for behavioural problems while their child is on high-dose corticosteroids. Proactive measures such as psychological and stress management support should be readily available at the treating centres.

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Table 1. Demographic information in both INS and control group (N = 140)

	N (%)		p value*
	INS (n=70)	Control (n=70)	
Gender			0.392
Male	43 (61.4)	38 (54.3)	
Female	27 (38.6)	32 (45.7)	
Race			0.496
Malay	70 (100)	68 (97.1)	
Others[+]	-	2 (2.9)	
Family income			0.757
< RM3000.00	49 (70)	43 (61.4)	
≥RM3000.00	21 (30)	27 (38.6)	
Education level			0.249
Primary	53 (75.7)	44 (62.9)	
Secondary	17 (24.3)	26 (37.1)	

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

Table 2. Clinical characteristics of children with INS (N=70)

	Mean (±SD)	n (%)	
Age at diagnosis (years)	5.77 (±2.86)		
Duration of illness (months)	51.60 (±37.54)		
Current dosage of steroid (mg)	22.50 (±19.41)		
Duration of steroid (weeks)	31.07 (±27.19)		
Medical Complications		Yes	No
Hypertension		25 (35.7)	45 (64.3)
Cataract		9 (12.9)	61 (87.1)
Cushingoid		9 (12.9)	61 (87.1)
Stunted growth		2 (2.9)	68 (97.1)

Table 3. Differences in CBCL total, major domains, and sub-scale scores between children with INS and controls (N=140)

	INS (n=70) Median (IQR)	Control (n=70) Median (IQR)	p value*
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

CBCL - Child Behavioural Checklist
* Mann-Whitney U Test

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

Psychological problems	Internalising	Externalising	Withdrawal	Somatic	Anxious	Aggressive
Duration	0.20	0.07	0.09	0.13	0.25*	0.00
Dosage	0.43**	0.17	0.50**	0.27*	0.44**	0.14

* p<.05
**p<.01
Spearman Correlation Coefficient

Table 5. The association between internalising problems with selected socio-demographic variables and clinical characteristics in children with INS.

Variables	SLR		MLR	
	Crude regression coefficient, b	p value	Crude regression coefficient, b	p value
Age	-0.12(-0.89,0.66)	0.763		
Gender Male Female	 0 2.51(-2.30,7.05)	 0.274		
Education level Primary Secondary	 0 -0.42(-5.62,4.78)	 0.873		
Family income <RM3000.00 ≥RM3000.00	 0 -2.46(-7.29,2.37)	 0.312		
Hypertension No Yes	 0 0.37(-4.28,5.02)	 0.873		
Cataract No Yes	 0 0.15(-6.51,66.81)	 >0.950		
Cushingoid No Yes	 0 15.71(10.24,21.18)	 <0.001*	 0 13.50(7.99,19.00)	 <0.001*
Stunted growth No Yes	 0 7.00(-6.27,10.27)	 0.296		
Duration	0.06(-0.02,0.14)	0.158		
Dosage	0.20(0.09,0.30)	<0.001*	0.13(0.03,0.22)	0.011*

* p<.05
SLR - Simple linear regression
MLR - Multiple linear regression

Table 6. The association between externalising problems with selected socio-demographic variables and clinical characteristics in children with INS.

Variables	SLR		MLR	
	Crude regression coefficient, b	p value	Adjusted regression coefficient, b	p value
Age	-0.72(-1.28,-0.15)	0.014*	-0.64(-1.18,-0.10)	0.021*
Gender Male Female	 0 -0.62(-4.13,2.89)	0.726		
Education level Primary Secondary	 0 -3.02(-6.93,0.90)	0.129		
Family income <RM3000.00 ≥RM3000.00	 0 -2.74(-6.40,0.94)	0.142		
Hypertension No Yes	 0 -2.03(-5.57,1.51)	0.256		
Cataract No Yes	 0 -1.67(-6.76,3.42)	0.515		
Cushingoid No Yes	 0 9.07(4.32,13.79)	<0.001*	 0 6.58(1.90,11.25)	 0.007*
Stunted growth No Yes	 0 0.16(-10.09,10.42)	>0.950		
Duration	0.02(-0.04,0.09)	0.471		
Dosage	0.07(-0.02,0.16)	0.120		

* p<.05
SLR - Simple linear regression
MLR - Multiple linear regression