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Cognitive and Behavioral Aspects in Children with Nephrotic Syndrome; Does it Need Special Attention

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Abstract

Purpose: This study was done to see and assess the cognitive and behavioral impairment in children with nephrotic syndrome and to find out any relationship with disease-specific or treatment specific characteristics.

Methods: This one-year case-control study was conducted from October 2018 to November 2019 among the diagnosed case of nephrotic syndrome, age range 3-16 year without an active stage of nephrosis or infection. Control groups were selected from age and sex-matched patients admitted in the same hospital after controlled active disease and without any chronic illness. The Wechsler Intelligence Scale for children (WISC) for assessment of Cognitive function was performed in both groups. Moreover, to assess behavioral impairment, the Strengths and Difficulties Questionnaire (SDQ) were performed in both groups.

Results: Among the case group steroid dependency was noted with 58.1% and about 27% received for prolong period (> 3months). A total cumulative dose before hospital admission was 384.16±206.94 mg/kg. All the domains of cognitive parameter and behavioral parameters affected significantly in nephrotic syndrome children than the control group($p<0.05$). Mostly affected cognition domains were verbal 72% and processing speed 74%. Considering behavioral parameters, conduct 44.2% and hyperactive 14.2% disorders were affected severely among these children. Both the cognitive and behavioral impairment were significantly affected by prolonged corticosteroid therapy($p<0.0001$).

Conclusion: Severe psychosocial and emotional impairment are commonly seen among those children who are getting steroid for a prolonged period, which argues in favor of a low threshold for switching to sparing drugs.

Keywords: Cognitive; Behavior; Children; Nephrotic syndrome.

Introduction

Cognitive and behavioral function has a vital influence on children's mental and emotional health. Cognitive impairment refers to a deficient thought process that leads to the problem in remembering, learning, concentrating and making decisions. Cognitive impairment can leads an individual to high risk of mental retardation and behavioral problems. So, it is very crucial to identify cognitive and behavioral impairment in early stages so that early interventions can be designed to prevent later occurrence of severe behavioral and emotional healthproblems.[1]

Nephrotic syndrome is primarily a pediatric disease with its long-drawn relapsing and remitting course. Due to the chronic nature of the illness,

children with nephrotic syndrome has various biological, behavioral, and social manifestations that have impact on social and mental health as well as future development of personality of the child.[2-4] Multiple factors can affect mental health as well as impaired quality of life in children with nephrotic syndrome,[5] which were related to side effects of medications,high dependence on medical equipment for a large part of life, dietary restriction, the unpredictability of relapse time, frequent periods of hospitalization.[6-8] Lack of physical growth and changes of self-image in the form of gum hypertrophy, hypertrichosis Moreover, and edema.[8-10] has adversely affect their social life.

Most of the nephrotic syndrome cases are sensitive to corticosteroid treatment which has various physical side effects that have been focused attention in multiple studies. However, the neuropsychiatric adverse effects of corticosteroids have received less attention. Moreover, the etiology and pathogenesis of these brain effects remain poorly understood. The neuropsychiatric adverse effects of corticosteroids are complex, unpredictable, and often severe, ranging across various categories of mood liability, anxiety symptoms, cognitive impairments, and behavioral disturbances.[11] Rates of psychiatric disturbance (predominantly depression and anxiety) in adults with Cushing disease are between 57% and 78%, while children with this disorder show rates of 44%, with predominating compulsive behaviors. The cause of the behavioral changes arising from steroid use is not known, but the involvement of some areas of brain such as hippocampus, the septum, and the amygdala have been implicated.[12] These areas of the brain have dense receptors for corticosteroids[13,14] and are involved in mood, behavior and memory functions of the brain. The hypoalbuminemia seen in nephrotic syndrome causes a high level of unbound prednisolone which will bind to the receptors in the earlier mentioned areas of the brain.[15] Corticosteroids are also known to alter brain excitability and affect the CNS levels of some neuropeptides and neurotransmitters leading to behavioral problems. The onset of symptoms varies from a few days to 4 weeks of commencing high dose steroids[16,17] and sometimes symptoms appear when the tapering of steroids commences due to their psychological dependency from their euphoric effects. The negative impact of prednisone on cognitive function, i.e. learning and memory retention, could be correlated with neuronal degeneration and reactive gliosis in brain regions which showed in a Vivo study in rats.[18]

The mainstay of treatment for steroid-induced psychosis is to reduce the dose of the steroid or discontinue it.[17,19] Psychoactive drugs have been used when discontinuation of steroids alone is not enough but with variable outcomes.[20] Risperidone have been used successfully and it has the advantage of rapidly acting even at low dose with absence of significant discontinuation syndrome. Electroconvulsive therapy has also been employed to treat psychosis in various cases and showed good response.[21]

Even though, it has been recognized that, children with nephrotic syndrome often experience significant emotional and behavioral problems.[22-25] avery few studies in India and abroad documenting the issues broadly.[26-30] Moreover, cognitive aspects of the children which is a very important issue but nearly missing in pediatric nephrology literature. In our country the mental and emotional health is still and neglected issue and scarcity of study in children regarding this aspect.

Therefore, our study aims to measure the prevalence of cognitive and behavioral problems in children with nephrotic syndrome compared to the healthy control group. It also aims to look into the association, if any, between cognitive and behavioral problems and sociodemographic as well as disease-related and treatment-related factors.

Materials and Methods

This case-control study was conducted in children between 3 to 16 year of age, who fulfilled the International study of kidney disease in children (ISKDC) criteria for the diagnosis of nephrotic syndrome [28]and admitted in Paediatric Nephrology Department of Dhaka Shishu(Children) Hospital From October 2018 to November 2019. Children with atypical Nephrotic Syndrome(either raised creatinine. raised blood pressure, gross hematuria or no response after 4 weeks of steroid therapy), secondary nephrotic syndrome, child with previous history of behavioral disorder, developmental delay, seizure disorder, thromboembolic disorder, hypothyroidism, enlarge adenoid or other associated chronic illness and also who had concurrent use of antihypertensive, antidepressant or anticonvulsant drugs were excluded from study. After correction of infection and active stage of nephrosis, informed written consent was taken from parents.

Detailed history taking including age and sex, socio-demographic status obtained from monthly income and educational level of parentsand careful examination including weight, height, BMI and blood pressure was assessed.For the case group duration of the disease, response totherapy, frequency of relapses, cumulative dose, and other complications of steroid therapy such as cushingoid features and evidence of cataract was detected with the help of the ophthalmology department of the National Institute of Ophthalmology(NIO).

To assess the general intellectual function and to find out the cognitive and learning delay of this child intelligence test was done by the Psychology department of the same hospital. The Wechsler Preschool and Primary Scale of Intelligence (WPPSI)- III edition test was designed for children age 3 years to 7 years 7 months old child which includes verbal, performance, processing speed, and full-scale domain. And for older children up to 16 years, Wechsler Intelligence Scale for Children (WISC)-IV was designed which includes verbal, processing speed, full scale, process reasoning and working memory as a domain. In order to assess children's emotional/behavioral problems, The Strengths and Difficulties Questionnaire (SDQ) was applied by the psychologist on the same day. SDQ is a brief behavioral screening questionnaire about 3-16-year-olds. All versions of the SDQ ask about 25 attributes, some positive and others negative. These 25 items are divided between 5 scales: 1) emotional symptoms (5 items), 2) conduct problems (5 items), 3) hyperactivity/inattention (5 items), 3) hyperactivity/inattention (5 items). The data were collected and analyzed thereafter.

Data Analysis

The data were analyzed according to standard procedure. SPSS Windows version 23.0 has been used for data analysis. Results of the findings were verified by doing standard tests for significance like Unpaired student "t" test, Man-Whitney test, Chi-Square (X2) tests, and finding out the p-value considering ≤0.05 as significant.

Results

The baseline clinical and demographic characteristics of case and control group are shown in Table 1. The duration of hospital stay is higher in the case group than in the control group p <.001.

Table 1: Clinical and Demographic Characteristics of case and control group.

	Case n=43	Control n=43	P value
Age (year)	5.89±2.52	5.62±2.35	0.708
Sex (M/F)	37.2/62.8	35.4/64.6	0.89
Socioeconomic status			
Low	20(46.5)	21(48.8)	0.92
Middle	19(44.2)	19(44.2)	
High	4(9.3)	3(7)	
Duration of hospital stay (days)	9.34±3.5	6.20±1.52	0.0003
BMI (SDS)	0.87±0.49	0.63±1.40	0.60
WAZ (SDS)	0.45±0.60	0.19±1.23	0.30
HAZ (SDS)	-0.742±0.67	0.523±0.66	0.0001

SDS-standard deviation score

Results were obtained by t test for quantitative variables and chi squarered test for qualitative variables considering p<0.05 significant at 95% confidence interval.

The disease and treatment characteristics of nephrotic syndrome children were depicted in Table 2. Among all varieties of nephrotic syndrome Steroid dependence, 58.1% was the most common form in the study Case group. About 27% of them were receiving prolong steroid therapy for more than 3 months. Cataract and cushingoid facies were found in 11.6% and 16.6% patients respectively. A total cumulative dose before hospital admission was384.16±206.94 mg/kg. Ongoing steroid dose during hospital admission was 18.13±6.17mg/kg. Out of them, 23% of nephrotic syndrome child was treated with an alternative agent such as levamisole, cyclophosphamide or CNI (Calcineurin Inhibitor).

Table 2: Disease and treatment characteristics of Case group.

Varieties of Nephrotic syndrome	n = 43
Initial episode	4(9.3)
IRNS	13(30.2)
SDNS	25(58.1)
FRNS	1(2.3)
Number of relapse	6.63±3.9
Prolong steroid therapy >3 month	12(27)
Duration of illness from onset-months	36.01±26.34 months
Cumulative dose- mg/kg (Before hospital stay)	384.16±206.94
Ongoing steroid- mg/kg (During hospital stay)	18.13±6.17
Other immunosuppressive	10(23)
Cataract	10(11.6)
Cushingoid facies	16(18.6)

Table 3: Cognitive parameter of Case and Control Group.

	Grading	Case n = 43	Control n = 43	P value
Verbal	1-average or more >/90	12 (27.9)	22 (51.2)	0.0001
	2-low average 80-89	10 (23.3)	21 (48.8)	
	3-borderline low 70-79	8 (18.6)	0 (00)	
	4-extreme low <70	13 (30.2)	0 (00)	
Processing speed	1-average >/90	11 (25.6)	33 (76.7)	0.0001
	2-low average 80-89	4 (9.3)	10 (23.3)	
	3-borderline 70-79	9 (20.9)	0 (00)	
	4-extreme low <70	19 (44.2)	0 (00)	
Performance	0-not performed	11 (25.6)	7 (16.3)	0.008
	1-average >/90	10 (23.3)	19 (44.2)	
	2-low average 80-89	7 (16.3)	13 (30.2)	
	3-borderline 70-79	8 (18.6)	4 (9.3)	
	4-extreme low <70	7 (16.3)	0 (00)	
Full scale	1-average >/90	19 (44.2)	38 (88.4)	0.0001
	2-low average 80-89	4 (9.3)	5 (11.6)	
	3-borderline 70-79	12 (27.9)	0 (00)	
	4-extreme low <70	8 (18.6)	0 (00)	
Working memory	0-not performed	33 (76.7)	36 (83.7)	0.482
	1-average >/90	6 (14.0)	6 (14.0)	
	2-low average 80-89	2 (4.7)	1 (2.3)	
	3-borderline 70-79	2 (4.7)	0 (00)	
	4-extreme low <70			
Process reasoning	0-not performed	33 (76.7)	36 (83.6)	0.372
	1-average >/90	4 (9.3)	5 (11.6)	
	2-low average 80-89	2 (4.7)	2 (4.7)	
	3-borderline 70-79	3 (7.0)	0 (00)	
	4-extreme low <70	1 (2.3)	0 (00)	

Table 4: Behavioural parameter of case and control group.

	Grade	Case n=43	Control =43	P value
Conduct	Normal	21 (48.8)	33 (76.7)	0.0001
	Borderline	2 (4.7)	0 (00)	
	abnormal	19 (44.2)	0 (00)	
Hyperactivity	Normal	34 (79.1)	32 (74.4)	0.003
	Borderline	2 (4.7)	1 (2.3)	
	abnormal	6 (14.0)	0 (00)	
Emotion	Normal	36 (83.7)	21 (48.8)	0.0001
	Borderline	2 (4.7)	12 (27.9)	
	abnormal	4 (9.3)	0 (00)	
Peer problem	Normal	36 (83.7)	26 (60.5)	0.001
	Borderline	2 (4.7)	7 (16.3)	
	abnormal	4 (9.3)	0 (00)	
Total	Normal	36 (83.7)	33 (76.7)	0.004
	Borderline	2 (4.7)	0 (00)	
	abnormal	4 (9.3)	0 (00)	
Prosocial	Normal	38 (88.4)	33 (76.7)	0.008
	Borderline	2 (4.7)	0 (00)	
	abnormal	2 (4.7)	0 (00)	

Results were obtained by chi squared test considering p<0.05 significant at 95% confidence interval.

NB: Child 3-7 year WIPSI -III- (Verbal,Performance,Processing speed, Full scale) Child>7 year- WISC -IV (Verbal, Processing speed, Full scale, Process reasoning, Working memory).

Table 3 showed all the domains of cognitive parameter verbal, processing, performance, and full scale was affected significantly in nephrotic syndrome children than the control group (p-value <.001). Working memory and process reasoning, these two domains which had done in a child more than 7 years were less affected. Among all domains of cognition, verbal 72%, and processing speed 74% affected vigorously in nephrotic syndrome child.

Among the behavioral parameters, a significant difference was found in Table 4 between the case and control group (P<.001). Conduct 44.2% and hyperactive 14.2% disorders were affected severely in nephrotic syndrome child.

In order to find out the co-relationship of disease-specific and treatment-specific variables, among cognitive parameters, significant verbal impairment was found with a high cumulative dose(p=0.017), a high number of relapse (p=0.048), and a prolonged period of steroid therapy**(p<0.001). Processing speed impairment significantly correlates with prolonged period of steroid therapy**(p<0.0001) and a high number of relapse (p=-0.017). Prolong disease process significantly alter performance skill, working memory and process reasoning. **(p<0.0001). Other cognitive parameters such as full scale and performance also had a significant correlation with prolonging steroid therapy and cumulative dose. (p<0.01)

Among the behavioral parameter, conduct disorder has a significant correlation with prolonging steroid therapy. **(p<0.0001). The hyperactive disorder has no significant relation with any factor. Emotion (p<-.01) and prosocial behavior (p<.001) have a significant relation to prolonging steroid therapy. Cumulative dose, duration of onset has no significant association with behavioral impairment.

Discussion

These case control study was done in a tertiary children hospital in Dhaka city to identify the cognitive and behavioral abnormalities of nephrotic syndrome children and their various association. This is an important observation that could affect a child's mental as well as emotional health. Due to complicated course and association of infection or other comorbidities, duration of hospital stays becomes longer in nephrotic syndrome child in comparison with control group which might have an impact on cognitive and behavioral impairment.

This study showed that cognitive impairment such as Verbal, processing speed, performance, and full-scale IQ significantly affected in nephrotic syndrome child than a control group. These findings were well matched with the findings of Manti et al.[33]

The result of this study showed behavioral impairment mainly conduct disorder, hyperactive, emotional disorder was seen more frequently in nephrotic syndrome children. This finding partly correlates with the study done by Mehta M which showed a significant number of nephrotic children's show features of depressed, hyperactive or aggressive behavior and the behavior abnormality scores correlated with the anxiety scores of the mothers of children with nephrotic syndrome.[30]

It was evident in our study that, prolong duration of steroid therapy, high cumulative dose and the frequent relapsing course has a significant role in cognitive impairment especially in verbal, processing speed, full scale, and performance IQ. Whereas the duration of illness has a positive correlation with working memory and process reasoning. Another study done by Manti et al showed no significant correlation with disease and treatment-specific variables in cognitive impairment. Some studies showed diminished verbal IQ in high steroid dose.[25] The cognitive impairment in our study may be overestimated due to dealing with a hospitalized patient in morbid condition which can affect the IQ of child. Besides,prolong steroid therapy may cause cushingoid facies, short stature, obesity and cataract that may play an important role in contributing to significant cognitive impairment.

It was found in this study that, prolong period of steroid therapy has played an important role in behavioral impairment. Surprisingly, there was

no significant association between corticosteroid treatment and behavior abnormality. However, the dose of corticosteroid received by most children in our study sample was steroid-dependent nephrotic syndrome and many are getting steroid in moderate to a low dose for a prolong time long time, so it is very difficult to conclude the dose or duration specific factor responsible for behavioral impairment. Studies that have reported a significant correlation between corticosteroid use and behavior problems also noted that the observed behavioral changes occurred almost exclusively at the higher dose ranges of prednisone. [15,20]. Additionally, another study by Guha M showed a significant association with a behavior problem in the nephrotic syndrome children with frequency of relapse and low socioeconomic status. [31,32,33]As most of the children's brought up from low socioeconomic status, increased frequency of relapse is associated with more frequent follow-up, adding to the financial burden of the already economically compromised households. This could possibly explain the significant association between the frequency of relapse and behavioral maladjustment.

Thus, while the growing literatureshowed the behavioral/psychosocial as well as cognitivealterations as the side effect of long-term steroid treatment, further research will be required to fully clarify the pathogenesis. The assessment of patient's cognition and behavior following cessation of steroid therapy may help to confirm that findings of behavioral change and cognitive change are steroid-related. The reassessment of the same patients over several episodes of relapse may explain the possibility of any sensitization effect of multiple courses of steroids.

Conclusion

Nephrotic syndrome children may experience behavioral and cognitive impairment in the course of their treatment. Prolong exposure to corticosteroid treatment has a positive correlation with cognitive as well as behavioral impairment. In clinical practice, minimizing long-term steroid treatment should be a constant goal in the follow-up of steroid-sensitive nephrotic syndrome children. Finally, future research may be warranted to reconsider the optimal steroid dose and therapy duration in an effort to optimize the benefit or risk the ratio in steroid-treated patients.

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