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Study of the Effects of Glucocorticoid on Growth and Adult Final Height in Children with Primary Nephrotic Syndrome

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Abstract

Objective: To analyze the epidemiological characteristics of growth, as well as factors associated with growth retardation in children with primary nephrotic syndrome (PNS), and to investigate the effect of glucocorticoid (GC) use duration on growth retardation in these children. **Methods:** Clinical and laboratory data of 353 PNS children treated at our hospital from July 2014 to June 2015 were collected through the medical record management system. Height, weight, and GC usage were recorded. Follow-up assessments were conducted in August 2022 for the original group, recording height, weight, and GC usage. Height and weight were evaluated using standard deviation scores (SDS). Categorical data were analyzed using chi-square test while continuous measurement data were analyzed using t-test or rank-sum test. Linear regression was used to assess the association between two single independent variables, and logistic regression analysis was used to screen for risk factors related to growth retardation in children with PNS. **Results:** Among the 353 PNS children enrolled in this study, male-to-female ratio of 2.64:1 (256 males vs 97 females). A total of 119 children exhibited growth retardation, incidence rate of 33.71%. The duration of GC usage among those with growth retardation was significantly longer compared to those without it (762.81 ± 934.50 days vs 263.77 ± 420.49 days; $p < 0.05$). There was a negative correlation between GC usage duration and height SDS ($r = -0.406$; $p < 0.05$). Telephone follow-up was conducted on 61 patients, with 14 (22.95%) exhibiting growth retardation. Among the 34 patients who reached final adult height, 11 (32.35%) was in the growth retardation group, accounting for 64.28% of the total growth retardation cases (9 out of 14). **Conclusion**: PNS children treated with GC have a high incidence of growth retardation, and a high

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proportion of short stature in adulthood, especially in children with growth retardation in childhood, most of them have short stature after grown up. Time of GC usage is a risk factor for growth retardation in children with PNS.

Keywords

Primary Nephrotic Syndrome, Glucocorticoid, Children, Growth Retardation, Adult Height

1. Background

The main clinical features of nephrotic syndrome (NS) are massive proteinuria, hypoalbuminemia, oedema, and hyperlipidemia. Glucocorticoid (GC) for the treatment, of nephrotic syndrome for 60 years, is still the primary first-line treatment for the primary nephrotic syndrome (PNS), children long-term use of GC's three most common adverse reactions are weight gain, Cushing syndrome, and growth re-tardation, the incidence of adverse effects of 22.4%, 20.6% and 18.9% [1]. There are clinical study data showing that the growth and development of PNS children with long-term GC treatment are affected to different degrees, and growth retardation can occur [2] [3] [4] [5] [6]. Growth retardation means that the height of an individual child is 2 standard deviations (−2.00 SD) below the same race, the same sex and the same age, or below the 3rd percentile [7]. Short stature can not only affect children's psychology, but also damage the quality of life, and affect self-esteem and social recovery in adulthood. There is a lack of multicenter big data epidemiological data reports on the growth and development of children with PNS, and no follow-up to adulthood to understand the height outcomes in adulthood.

In this study, we collected relevant clinical data, laboratory data, recorded growth and development indicators, GC use, and followed up the adult height level and GC use of children with PNS, and explored the epidemiological characteristics and related influencing factors of PNS, so as to provide reference for future treatment.

2. Methods

By searching the medical record management system of our hospital, the relevant clinical data and laboratory data of PNS children treated in our hospital from July 2014 to June 2015 were collected, and the growth indicators and GC usage of the children were recorded. The enrolled children were followed up by telephone in August 2022, and their height, weight, and GC usage were recorded.

Inclusion criteria: 1) met NS diagnostic criteria: massive proteinuria (24-hour urinary protein quantification 50 mg/kg), hypoproteinemia (plasma albumin < 25 g/L), with or without hyperlipidemia (plasma cholesterol > 5.7 mmol/L) and varying degrees of edema; 2) <18 years at diagnosis; 3) excluded children with

secondary nephrotic syndrome, congenital nephrotic syndrome, persistent low complement C3 and complement C4 levels, or chronic renal insufficiency.

Growth retardation definition: the height of an individual child is 2 standard deviations (−2.00SD) below the average height of the same race, sex or below the 3rd percentile in similar living environments.

After searching "diagnosis: primary nephrotic syndrome" in the medical record management system of our hospital, 353 children were eligible for enrollment, and clinical data were collected and recorded: height, height, SDS, weight, weight, SDS and BMI; GC treatment; and laboratory data: urine protein, 24-hour urine protein, blood creatinine, cystatin C, urea, uric acid, plasma total protein, plasma albumin, plasma globulin, total cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, blood calcium, blood phosphorus, 25 hydroxyvitamin D. Clinical data, laboratory data and treatment of children in the non-growth retardation and growth retardation group were compared. Group differences between different GC response types, different GC use times and different GC cumulative doses were analyzed. In August 2022, the height, weight and hormone use were recorded.

Statistical analysis: The pediatric data are expressed as mean ± SD, median and range or percentage. For categorical data, chi-square test, t-test or rank-sum test. Linear regression was used to assess the association between two single independent variables, multivariable analysis adjusted for potential confounders, and logistic regression analysis was used to screen risk factors associated with growth retardation in children with PNS. Risk factors were described as odds ratios (odds ratio, OR) and 95% confidence intervals (confidence intervals, CI). All data results were collated and analyzed using SPSS 13.0 statistical software, with $\alpha = 0.05$.

3. Results

3.1. Growth of the Children with PNS

The general clinical data of 353 children with PNS are eligible for follow-up treatment in our hospital of 234 children in 66.29%, and 119 in 33.71% (Table 1). There were 256 male children and 97 female children. The male-to-female ratio in the growth retardation group was 85:34, and that in the non-growth retardation group was 171:63. There was no statistical difference in the 2 groups (Table 1). The age of PNS onset was 4.06 ± 2.8 years old, and 3.97 ± 3.04 years old, p = 0.786, and there was no statistical difference between the groups.

The height SDS in the growth and non-retardation group were −3.16 ± 1.05 and −0.69 ± 1.05, p < 0.001; compared with the BMI and SDS in the non-retardation group, p < 0.001 **(see Table 1 for details)**.

Laboratory data for the children with PNS are shown in Table 2, 24 h 2.69 ± 2.90 g/24h, Plasma albumin was 21.23 ± 11.84 g/L, Globulin, 25.74 ± 5.43 g/L, Creatinine at 31.78 ± 21.18 umol/L, Cystatin C 0.82 ± 0.34 mg/L, Uric acid 346.01 ± 131.26 umol/L, Total cholesterol was 9.64 ± 3.64 mmol/L, 25 Hydroxyvitamin D 26.98 ± 17.00 mmol/L, Blood calcium 1.94 ± 0.36 mmol/L, Blood

Table 1. General clinical characteristics of children with PNS at baseline.

	Total	non-growth retardation group	Growth retardation group	p
N, (%)	353	234, (66.29%)	119, (33.71%)	
Boy: girl	256:97	171:63	85:34	p = 0.743
Age of onset	4 (1,13)	4 (1,12)	3 (1,13)	p = 0.786
Age of Enroll	7 (1,15)	6 (1,14)	9 (1,15)	p = 0.011
24 hr urine protein, (g/24h)	2.69 ± 2.90	2.84 ± 3.15	2.40 ± 2.33	p = 0.191
Urine acid, (umol/L)	346.01 ± 131.26	339.69 ± 136.19	358.05 ± 121.35	p = 0.220
Creatinine, (umol/L)	31.78 ± 21.18	31.69 ± 23.74	32.02 ± 15.22	p = 0.892
Cystatin C, (mg/L)	0.82 ± 0.34	0.80 ± 0.28	0.85 ± 0.43	p = 0.151
Albumin, (g/L)	21.23 ± 11.84	23.76 ± 15.47	19.97 ± 9.24	p = 0.016
Globulin, (g/L)	25.74 ± 5.43	25.62 ± 6.27	25.98 ± 3.26	p = 0.485
Cholesterol, (mmol/L)	9.64 ± 3.64	9.53 ± 3.52	9.79 ± 3.82	p = 0.530
25-hydroxyvitamin D, (mmol/L)	26.98 ± 17.00	26.59 ± 16.68	27.75 ± 17.65	p = 0.562
Calcium, (mmol/L)	1.94 ± 0.36	1.93 ± 0.41	1.97 ± 0.22	p = 0.317
Phosphorus, (mmol/L)	1.54 ± 0.41	1.55 ± 0.44	1.50 ± 0.32	p = 0.274
Ht SDS	−1.52 ± 1.62	−0.69 ± 1.05	−3.16 ± 1.05	p < 0.001
Wt SDS	0.21 ± 1.12	0.61 ± 0.98	−0.47 ± 1.01	p < 0.001
BMI SDS	1.06 ± 1.97	1.29 ± 1.50	0.53 ± 2.73	p < 0.001
GC usage time, (d)	335 (0, 3448)	232 (0, 1557)	702 (39, 3448)	p < 0.001

Table 2. Clinical characteristics of children with PNS at follow-up.

	Total	non-growth retardation group	Growth retardation group	p
Enroll				
N, (Boy: girl), n	61, (42:19)	43, (28:15)	18, (14:4)	
Age	7 (1,15)	6 (1,14)	9 (1,15)	p < 0.05
Ht SDS	−1.31 ± 1.69	−0.54 ± 1.28	−3.165 ± 0.97	p < 0.001
GC usage time	720.04 ± 827.67	468.27 ± 487.08	1010.54 ± 1045.90	p < 0.001
Follow-up				
Age	15 (9, 26)	15 (9, 26)	18 (13, 24)	p < 0.05
Ht SDS	−1.12 ± 1.83	−0.54 ± 1.39	−2.47 ± 2.06	p < 0.001

Continued

Retardation, n, (Boy: girl)	14, (12:2)	3, (3:0)	11, (9:2)	$p < 0.001$
GC usage time	1441.14 ± 943.56	1126.53 ± 987.08	1904.15 ± 787.78	$p < 0.001$
Total GC usage time	2161.18 ± 1483.98	1594.80 ± 1218.89	2814.69 ± 1535.57	$p < 0.001$
*Final height, n, (Boy: girl)	34, (25:9)	20, (14:6)	14, (11:3)	
Final height SDS	−1.69 ± 2.08	−0.81 ± 1.61	−2.89 ± 2.08	$p < 0.001$
Final height short stature, n	11	1	10	$p < 0.001$

*Final height: boy ≥ 18 years old, girl ≥ 16 years old.

phosphorus was 1.54 ± 0.41 mmol/L. Plasma albumin 23.76 ± 15.47 g/L was lower than 19.97 ± 9.24 g/L, $P < 0.05$; among other laboratory indicators, $p > 0.05$.

3.2. Time of GC Usage in Children with PNS

The mean GC use time of the children was 114.5 ± 681.14 days. The GC use time between the growth retardation group and non-growth retardation group was 762.81 ± 934.50 days and 263.77 ± 420.49 days, respectively, $p < 0.05$; indicating the significantly prolonged duration of GC use in the growth retardation group (see the Table 2).

The results of uni-variate analysis showed that the correlation coefficient of GC use time was $r = -0.406$, $p < 0.05$, and the time of GC use was associated with height SDS in children with PNS.

Using multivariate analysis to adjust for potential confounders, logistic regression analysis of growth retardation in children with PNS showed that OR for time = 1.782, 95% CI (1.401, 2.267), $p < 0.001$; indicating that duration of GC use was a relevant risk factor for growth retardation in children with PNS.

3.3. Growth of Children with PNS after 8 Years

In August 2022, two children were followed by telephone, and 61 patients with male to female ratio of 42:19, 43 in the non-growth retardation group and 18 in the growth retardation group.

Age at enrollment was 6.34 ± 3.85 and 9.01 ± 3.83, $p < 0.05$, a significant difference, and the growth retardation group was older. The height SDS at the time of enrollment was −0.54 ± 1.28 for non-growth retardation and −3.165 ± 0.97, $p < 0.001$, and GC use time was 468.27 ± 487.08, 1010.54 ± 1045.90, respectively, $p < 0.001$.

At telephone follow-up, age was 13.07 ± 4.03 and 15.78 ± 3.57, respectively, $p < 0.05$, were statistically significant and the growth retardation group was still older. In the non-growth retardation group, the height SDS was −0.54 ± 1.39, and the height SDS of the growth retardation group was −2.47 ± 2.06, $p < 0.001$.

Of the 61 children, 14 were growth retarded, or 22.95%, including 3 in the non-growth retardation group and 11 in the growth retardation group, $p < 0.001$. The GC usage time was 1126.53 ± 987.08 and 1904.15 ± 787.78, respectively, $p < 0.001$. Total cumulative GC use time was 1594.80 ± 1218.89, 2814.69 ± 1535.57, $p < 0.001$, respectively.

At the time of telephone follow-up, 34 cases (male: female = 25:9) reached their final height (18 years old men, 16 years old women), including 20 in the non-growth retardation group, 14 in the growth retardation group, height SDS was −1.69 ± 2.08, height SDS was −0.81 ± 1.61, and height SDS was −2.89 ± 2.08, $p < 0.001$. Among the 34 patients, 11 patients, accounting for 32.35%, were 9 patients in the growth retardation group, accounting for 64.28% in the total growth retardation group (9:14).

4. Discussion

NS is a common glomerular disease in children. It has been reported that the annual incidence of NS in children is 2 - 16.9/100,000. The incidence of NS in different races, countries and regions is different, and the ratio of male to female is 1.91 - 2.50:1 [6]-[11]. In this study, the male-to-female ratio of 353 children with PNS was 2.64:1, the male-to-female ratio of non-growth retardation group was 2.71:1, and the male-to-female ratio of growth retardation group was 2.50:1. There was no significant difference in gender between the groups, suggesting that there was no correlation between growth retardation and gender in children with PNS. The average age of onset was 5.31 ± 3.46 years. The age of onset in the growth retardation group was 3.97 ± 3.04 years, which was lower than that in the non-growth retardation group (4.06 ± 2.80 years, $p = 0.786$), suggesting that the growth retardation in children with PNS was not related to the age of onset. The average age of children with growth retardation (6.13 ± 3.74 years) was higher than that of children without growth retardation (5.12 ± 3.42 years), $p < 0.05$, the difference was statistically significant, suggesting that PNS children with an onset age of less than 3.97 years old who still received GC treatment after 6.13 years old had a higher risk of height SDS loss.

According to the literature, among the diseases requiring long-term GC treatment, the incidence of growth retardation in children is 18.9% [1], which is one of the most common adverse reactions of GC. Research data show that the incidence of growth retardation in the normal population is 1.3% - 20.9%, and the incidence of growth retardation in hospitalized children in developed countries is 2% - 24% [12] [13]. Research data in the United States show that the incidence of growth retardation in child health care institutions is 5% - 10%, and the incidence of growth retardation in hospitalized children is 3% - 5% [14]. No epidemiological data of growth retardation in normal population has been reported in China. The results of this study show that, the height SDS of PNS children was −1.52 ± 1.62, and the average height SDS of PNS children was lower than that of normal children of the same race, sex and age [15]. The height of PNS children was shorter than that of normal children. The incidence of growth

retardation in children with PNS (33.71%) was higher than that in the normal population (1.3% - 24.0%) and in children requiring long-term GC treatment (18.9%). pediatricians should paid attention to PNS related growth retardation.

The results showed that there was no statistical difference between growth retardation group and non-growth retardation group in 24-hour urine protein and plasma globulin, $p > 0.05$ (see Table 1). Plasma albumin of children with growth retardation group and non-growth retardation group was 23.76 ± 15.47 g/L and 19.97 ± 9.24 g/L, $p < 0.05$, suggesting that the severity of hypoproteinemia was related to growth retardation of children with PNS. The creatinine, cystatin C and uric acid of the children enrolled in this study were all in the normal range. The results in our study showed that calcium and vitamin D levels in children with PNS were lower than normal range, suggesting that low calcium and vitamin D levels were one of the factors affecting growth and development of children with PNS.

The uni-variate analysis in this study revealed a significant negative correlation ($r = -0.406$, $p < 0.05$) between GC usage time and height SDS, indicating that prolonged use of GC is associated with decreased height SDS and growth retardation in children with PNS. Furthermore, the odds ratio (OR = 1.782, 95% CI: 1.401 - 2.267, $p < 0.001$) suggests that the duration of GC usage is a relevant risk factor for growth impairment in these patients. Therefore, it is crucial for pediatricians to be aware of the potential impact of GC on children's growth when managing nephrotic syndrome cases and prioritize strategies aimed at reducing their use.

Among the 61 children followed by telephone, 14 were growth retarded, accounting for 22.95%, including 3 in non-growth retardation group and 11 in growth retardation group, $P < 0.001$, indicating that the incidence of growth retardation decreased slightly with age and the improvement of primary disease, but still about one-fifth children had growth retardation. Among the 34 patients who reached their final adult height, 11 patients had short final stature, accounting for 32.35%, indicating that one-third of the children with PNS had final adult short stature. Within this subgroup, there were 9 cases in the growth retardation group, accounting for 64.28% (9:14) of the total growth retardation group, indicating that 2/3 of the children with growth retardation in childhood continued to be short in adulthood. It is crucial for pediatricians to be aware of early signs and intervene promptly regarding growth development among these children.

Although this study involved an eight-year follow-up, it is important to note that due to limitations associated with telephone follow-ups and studied at a single center, statistical errors may have occurred. We should involve close monitoring and multi-center to minimize potential statistical errors.

5. Conclusion

In conclusion, children with PNS treated with GC have a higher incidence of growth retardation and a high proportion of short stature in adulthood, particu-

larly in those who experienced growth retardation during childhood and most of them have short stature in adulthood. Furthermore, the duration of GC usage is closely associated with the growth outcomes in children with PNS. Therefore, time of GC usage is a risk factor for growth retardation in children with PNS. This study reminds pediatricians that when treating children with nephrotic syndrome, they should minimize the use of GC and pay close attention to the height of children. It also provides a basis for the treatment of growth retardation in children with nephrotic syndrome.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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