

## Growth Delay in Steroid Sensitive Nephrotic Patients

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### ABSTRACT:

#### BACKGROUND:

Growth in patients with idiopathic nephrotic syndrome (INS) is influenced by several factors, they suffer the influence of the disease itself as long as there is proteinuria, caused by the increase of the glomerular permeability and leading to hypoproteinemia. The effects of the glucocorticoid treatment, which alters growth by a direct action on the growth cartilage, or via disturbances of growth factors. In this study we assess the effect of nephrotic syndrome, its relapse rate and its treatment (i.e. steroid), in the statural growth of steroid sensitive nephrotic patients.

#### METHODS:

A Prospective study of 110 steroid responsive nephrotic patients collected from AL- Kadhemia Teaching Hospital, Central Child Teaching Hospital, Child Wellfare Teaching Hospital & AL-Karama Teaching Hospital. The study started from first of June 2005 to first of June 2006. Data collected as following: age, sex, date of first diagnosis, duration of disease, number of relapses per year, measurement of the height, weight and body mass index and sign of steroid toxicity.

#### RESULTS:

Total number of our patients were 110, 74(67.3%) were males and 36(32.7%) were females, with male to female ratio of 2:1. The age of our patients range from 2-18 years with a mean of 7.9+3.8 years. Thirty-one (28.2%) of them were with height below 3<sup>rd</sup> percentile for their age, 24(77.4%) were males and 7(22.6%) were females. Twenty-five (22.7%) patients were at pubertal age. Eighteen (72%) were males and 7(28%) were females, and 17(68%) of them have height below 3<sup>rd</sup> percentile. Seventy-six (69%) patients have their onset of the disease at age between 2 and 6 years. Forty-six (41.8%) of patients have disease duration of less than 3 years, 3 (6.5%) of them were have height below 3<sup>rd</sup> percentile, 46(41.8%) with duration of 3-6years, 14(30.4%) them were have height below 3<sup>rd</sup> percentile and 18(16.4%) with duration of more than 6 years, 14(77.8%) of them have height below 3<sup>rd</sup> percentile. Fifty-five (50%) patients had frequent relapses, twenty-seven (49.1%) of them have height below 3<sup>rd</sup> percentile, compared to 4(7.3%) of those with infrequent relapse had height below 3<sup>rd</sup> percentile. Forty-seven (42.7%) patients show sign of steroid toxicity (cushigoid facial appearance with or without hypertension, obesity, hirsutism. etc) 25(53.2%) of them have height below 3<sup>rd</sup> percentile, compared to 6(9.5%) of those who have no sign of toxicity.

#### CONCLUSION:

Nephrotic syndrome is a potentially chronic disease with patients suffering a relapsing course and being at risk of frequent courses of prednisolone therapy with increase the risk of growth delay especially in patients reaching pubertal age and still taking steroid therapy.

**KEY WORD:** (Growth Delay, Steroid, Nephrotic).

### INTRODUCTION:

Nephrotic syndrome is a clinical syndrome of massive proteinuria defined by:

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Proteinuria (albuminuria) of more than 40 mg/m<sup>2</sup>/hr (more than 1g/m<sup>2</sup>/day), or an early urine protein to creatinine index of more than 3.5mg/mg. Edema. Hypoalbuminemia of less than 25g/l (2.5 g/dl).

Hypercholesterolemia . (1, 2) And lipiduria.(3). It is a disorder of glomerular perm-selectivity that may be primary (idiopathic) or secondary to an overt systemic diseases. The most common form of nephrotic syndrome in children is Minimal Change Nephrotic Syndrome (MCD), accounts for 90% of nephrotic syndrome in children, which is associated with minimal histologic glomerular changes by light

microscopy.<sup>(1, 2, 4)</sup> Minimal change disease is also defined by response to corticosteroid therapy — that is, as Steroid -Responsive Nephrotic (SRNS). Less common forms of nephrotic syndrome in children are resistant to corticosteroid therapy. Among these, Focal Segmental Glomerular Sclerosis (FSGS) is usually indistinguishable clinically from MCD except for its lack of response to corticosteroid therapy and its significantly poorer prognosis.<sup>(1-7)</sup>

**PATHOPHYSIOLOGY:**

Heavy proteinuria (albuminuria) is the hallmark of this condition and the primary abnormality in NS. The degree of proteinuria varies considerably from one child to another. Some children will excrete as much as 15 g/m<sup>2</sup>/24 hours, and the minimal excretion compatible with the diagnosis is around 1 g/m<sup>2</sup>/24 hours (approximately 40 mg/m<sup>2</sup>/hour). The initiating event that produces proteinuria remains unknown.<sup>(5, 6)</sup> In INS, the glomerular capillary permeability to albumin is selectively increased, and this increase in filtered load overcomes the modest ability of the tubules to reabsorb protein. Part of this increase in albumin excretion may be because of the smaller size of the albumin molecule, but since the excretion of some even smaller weight plasma proteins is not proportionally increased, the presence of other factors is obvious.<sup>(7)</sup>

**GROWTH:** Growth in patients with idiopathic nephrotic syndrome (INS) is influenced by several factors. Before the onset of the disease, children with nephrotic syndrome undergo the same influences as the general population. Afterwards, they suffer the influence of the disease itself as long as there is proteinuria, caused by the increase of the glomerular permeability and leading to hypoproteinemia, associated with urinary loss of several substances important for growth.<sup>(19, 20)</sup> Hypothyroidism due to loss of thyroxin binding globulin (thyroid hormone stimulated both cartilage proliferation & epiphyseal differentiation)<sup>(21)</sup>. The massive loss of urinary protein induces a degree of protein malnutrition in all children with NS.<sup>(19, 20, 21, 22)</sup> After initiation of steroid therapy, in most cases the protein losses regress quickly. This leaves only the effects of the glucocorticoid treatment, which alters growth by: a. Direct action on the growth cartilage<sup>(22, 25)</sup> or b. Disturbances of growth factors<sup>(26, 27)</sup>.

Glucocorticoids in pharmacological doses inhibit growth in humans, however this effect seems to be variable and not uniform among different subjects. However this effect seems to be variable and not

uniform among different subjects. These inhibitory effects on growth might be the result of:

**1-** Inhibition of growth hormone (GH) release, directly on the pituitary somatotrophs or through inhibition of growth hormone releasing hormone (GHRH).<sup>(25, 26)</sup>

**2-** Inhibition of insulin-like growth factor (IGF-I) response to GH stimulation<sup>(25, 26)</sup> and/or

**3-** Inhibition of GH or IGF-I action on the chondrocytes of the epiphyseal growth plate.<sup>(23, 24)</sup>

In addition glucocorticoids interfere with chondrocyte growth and enchondral bone formation. They inhibit sulfate incorporation into cartilage matrix as well as mineralization and formation of new bone<sup>(21)</sup>. In cultured epiphyseal chondrocytes, dexamethasone decreases DNA synthesis and cell proliferation; growth hormone receptor expression, and paracrine IGF-1 secretion<sup>(21)</sup>.

Also they reduce calcium absorption in the intestine and enhance urinary excretion of calcium<sup>(21)</sup>. Investigation of the endocrine function of boys with steroid-sensitive nephrotic syndrome has shown an alteration in the hypothalamic-hypophyseal-gonadal axis related to glucocorticoid use, which is responsible for the retarded growth<sup>(26)</sup>. Gonadotropic hormone axis stimulate and finally terminate body growth in puberty by direct action on the growth cartilage and by modulation of the somatotrophic hormone axis.<sup>(21)</sup>

Frequent relapsers have high chance to develop growth delay.<sup>(17, 28)</sup>

**AIM OF THE STUDY:** in this study we assess the effect of nephrotic syndrome, its relapse rate and its treatment (i.e. steroid), in the statural growth of steroid sensitive nephrotic patients.

**PATIENTS AND METHODS:**

A Prospective study of 110 steroid responsive nephrotic patients collected from AL- Kadhemia Teaching Hospital, Central Child Teaching Hospital, Child Wellfare Teaching Hospital & AL-Karama Teaching Hospital. The study started from first of June 2005 to first of June 2006. Data collected as following: age, sex, date of first diagnosis, duration of disease, number of relapses per year, measurement of the height, weight and body mass index and sign of steroid toxicity. Nephrotic syndrome defined as Proteinuria more than 40 mg/m<sup>2</sup>/hr (>1g/m<sup>2</sup>/day), edema, hypoalbuminemia of less than 25g/l and Hypercholesterolemia.<sup>(1, 2, 3)</sup> Response defined as protein free urine (less than 1+ on Albustix strips or less than 4mg/hr/m<sup>2</sup> of body surface area for at least one week) in all of at least three urine samples obtained within one week.

(1, 2, 3) Steroid responsiveness defined as complete remission within 8 weeks of prednisolone 2mg/kg/day, persisting for at least 2 months after termination of treatment.<sup>(1, 2, 3)</sup> Relapse defined as recurrence of proteinuria (3 or 4 on qualitative testing, or more on albutix strips) on at least 3 consecutive days after urine are protein free for 1 month.<sup>(1, 2, 3)</sup> Frequent relapse defined as 2 or more episodes within 6 months of initial response to treatment or 4 or more relapses within any 12 months period.<sup>(1, 2, 3)</sup> Steroid dependence was defined as recurrence of proteinuria within 2 weeks of discontinuation of prednisolone, or when the dose was lowered below a critical level.<sup>(1, 2, 3)</sup>

Height measured by stadiometer machine with standing height measured as follows: the child should stand straight and tall with heel firmly on the floor, the head is held so that he looks straight forward with the lower border of the eye sockets in the same horizontal plane as the external auditory meati, the patient should stretch his neck to be as tall as possible, then the child should in and out breaths, whilst gentle upward pressure is exerted upon the mastoid process then the maximum height is taken.<sup>(33)</sup> Height expressed in Tanner chart and the patient regarded as short if the height is below the third percentile of his /her age.<sup>(33)</sup> The height of patients diagnosed before June, 2005 is taken from their record and if not presents the patient is excluded from the study, also pts who have height below 3rd percentile at initial time of diagnosis are excluded. The weight of the patients also taken in the same way, but not included in the study as patients are overweight due to edema at time of relapse or as result of steroid toxicity.

<sup>(33, 34)</sup> Body mass index measured as body weight in kg/height in m<sup>2</sup> and the result is expressed in the chart of BMI for age, patient regarded as having obese if his /her BMI is more than 95% for the age.<sup>(35,36)</sup> Cushingoid facial appearance is the predominant sign of steroid toxicity which taken in account to gather with hypertension or obesity (BMI >95% for age), acne, hirsutism, cataract...etc. Treatment regimen; generally prednisolone used for treatment of the initial attack of nephrosis and for the relapses. PRD in 2mg/kg/day (60mg/m<sup>2</sup>/day) used initially for 4 weeks and if response occurs, then the dose is given for another 4 weeks but as an alternate day regimen and continues for about 3-4 months in tapering manner by 15mg/m<sup>2</sup>/2weeks.

Relapse treated in same way with changing to alternate day dose when the urine become free of albumine (i.e. nil, trace or 1+) for 3 consecutive days.

The alternate day dose may extend for 6-12 months in frequent relapses. In cases when steroid side effects appear, the alternative agent is used, cyclophosphamide (orally or as intravenous pulses) for 12 weeks in 2mg/kg/day dose, is commonly used. Other used cyclosporine A in a dose of 5mg/kg/day orally in 2 divided doses. In this study the major factors that affect the growth in patients with steroid responsive nephrotic patients (duration of the disease, steroid toxicity, frequent relapses) are studied using number, percentage and mean +SD, and analyzed by using statistical package for social science (SPSS 10). Associations between discrete variables measured by using Chi-Square test. P value less than 0.05 considered to be significant.

### **RESULTS:**

Total number of our patients were 110, 74(67.3%) were males and 36(32.7%) were females, with male to female ratio of 2:1. Age of our patients range from 2-18 years with a mean of 7.9+3.8 years.

Thirty-one (28.2%) of them were with height below 3<sup>rd</sup> percentile for their age, 24(77.4%) males and 7(22.6%) females; compared to 79(71.8%) of them having height above or equal to 3<sup>rd</sup> percentile for age. (Table1). Twenty-five (22.7%) patients were at pubertal age, 18 (72%) were males and 7(28%) were females, and 17(68%) of them have height below 3<sup>rd</sup> percentile. (Table2). Seventy-six (69%) patients have their onset of the disease at age between 2 and 6 years, 46 (41.8%) of patients have disease duration of less than 3 years, 3 (6.5%) of them with height below 3<sup>rd</sup> percentile. Forty-six (41.8%) with duration of 3-6 years, 14(30.4%) of them with height below 3<sup>rd</sup> percentile and 18(16.4%) with duration of more than 6 years, 14(77.8%) of them have height below 3<sup>rd</sup> percentile (Table 3). Fifty-five (50%) patients were have frequent relapses, 42(76.4%) were males and 13(23.6%) were female. twenty-seven (49.1%) of them have height below 3<sup>rd</sup> percentile, compared to 4(7.3%) of those with infrequent relapse were have height below 3<sup>rd</sup> percentile.

(Table 4) Forty-seven (42.7%) patients show sign of steroid toxicity, 38 (80.9%) were males and 9 (19.1%) were females, 25(53.2%) of them have height below 3rd percentile, compared to 6(9.5%) of those who have no sign of toxicity. (Table 5)

**Table 1: Relation of height to sex:**

Height	male	female	Total
>3 <sup>rd</sup> percentile	50(63.3%)	29(36.7%)	79(100%)
<3 <sup>rd</sup> percentile	24(77.4%)	7(22.6%)	31(100%)
Total	74(67.3%)	36(32.7%)	110(100%)

P value=0.115

Table (1) show that sex has no significant relation to statural growth and the differences are due to small number of females.

**Table 2: Relation of height to puberty:**

Height	Pre-pubertal	Pubertal	Total
>3 <sup>rd</sup> percentile	71(89.9%)	8(10.1%)	79(100%)
<3 <sup>rd</sup> percentile	14(45.2%)	17(54.8%)	31(100%)
Total	85(77.3%)	25(22.7%)	110(100%)

P value = 0.0001

Table (2) shows a significant relation between pubertal age and height, with height more affected in pubertal patients. pre-pubertal patients also affected in significant percentage.

**Table 3: Relation of height to duration of nephrotic syndrome:**

Height	Duration <3y	Duration 3-6y	Duration >6y	Total
>3 <sup>rd</sup> percentile	43(54.4%)	32(40.5%)	4(5.1%)	79(100%)
<3 <sup>rd</sup> percentile	3(9.6%)	14(45.2%)	14(45.2%)	31(100%)
Total	46(41.8%)	46(41.8%)	18(16.4%)	110(100%)

P value = 0.0001

Table (3) shows the significant relation between the prolong course of the disease and the delay in the statural growth.

**Table 4: Relation of height to relapse rate:**

Height	Infrequent relapses	Frequent relapses	Total
>3 <sup>rd</sup> percentile	51(64.6%)	28(35.4%)	79(100%)
<3 <sup>rd</sup> percentile	4(12.9%)	27(87.1%)	31(100%)
Total	55(50.0%)	55(50.0%)	110(100%)

P value: 0.0000007

Table (4) shows the significant relation of statural growth retardation with frequent relapse rate.

**Table 5: Relation of height to steroid toxicity:**

Height	Steroid toxicity +ve	Steroid toxicity -ve	Total
>3 <sup>rd</sup> percentile	22(27.8%)	57(72.2%)	79(100%)
<3 <sup>rd</sup> percentile	25(80.6%)	6(19.4%)	31(100%)
Total	47(42.7%)	63(57.3%)	110(100%)

P value =0.00007

Table (5) shows significant relation of statural growth delay to steroid toxicity.

**DISCUSSION:**

Growth in patients with idiopathic nephrotic syndrome (INS) is influenced by several factors. Before the onset of the disease, children with nephrotic syndrome (NS) undergo the same influences as the general population. Afterwards, they suffer the influence of the disease itself as long as there is proteinuria, caused by the increase of the glomerular permeability and leading to hypoproteinemia, associated with urinary loss of several substances important for growth (19, 20).

After initiation of steroid therapy, in most cases the protein losses regress quickly. This leaves only the effects of the glucocorticoid treatment, which alters growth by a direct action on the growth cartilage (21, 22) or via disturbances of growth factors. (25, 26) In our study, we found that boys are affected more than girls with male to female ratio of 2:1 which consistent with other studies like Bern J et al study. (16) we found that 28% of our patients having height below 3<sup>rd</sup> percentile for the age and this consistent with that found in Kitamura M study that shows 30% of his patients with FRNS having final height below M-2SD (28). In Renee et al study, they found that patients receiving corticosteroids had  $5.3\% \pm 0.7\%$  shorter stature than controls compared with the placebo group, whose stature was  $1.9\% \pm 0.8\%$  shorter than that of controls ( $p < 0.02$ ). (10) We also found that pubertal patients were more affected than the pre-pubertal, were about 55% of the pubertal patients having height  $< 3^{\text{rd}}$  percentile, compared to 45% in the pre-pubertal. This result consistent with that in Francesco Emma et al study which show of 12 patients that received PRD during puberty, 10 (83%) had a final height lower than their target compared with 4 of 11 (36%) of those that were no longer on steroid treatment before entering puberty ( $P < 0.03$ ) and conclude that adolescent patients treated with PRD during puberty experienced significant growth stunting despite being treated with considerably less PRD than pre-pubertal children. (20) This also consistent with Kitamura M study that shows final heights of boys receiving the steroid from 12 to 16 years of age and of girls treated with the steroid from 10 to 14 years of age were below M-2SD and 10 cm lower than the target height. (28) Also in the Rees L et al study the boy height decreased significantly only after the age of 10 years and was associated with delay in the appearance of secondary sexual characteristics (19). These results suggest that pubertal growth may be particularly sensitive to steroid treatment or that a cumulative effect resulting from

protracted steroid therapy is more apparent during adolescence. Also we found that pubertal males are affected more which also consistent with the Rees L et al study which show that there was a significant negative correlation between height and duration of treatment in boys, but not in girls. (19) Regarding the duration of nephrotic syndrome we found that about 90% of affected patients have disease duration of more than 3 years, compared to only 10% with disease duration less than 3 years this also consistent with the previous study which show that young children receiving PRD for more than 6 months per year were at considerably higher risk of experiencing severe growth stunting. Children with early onset nephrotic syndrome also appear to be at higher risk of growth retardation because they experience longer disease courses. (20) Relapse rate also of a significant role in growth delay, as our study show that 55 of our patients have frequent relapses, of them 27(49%) having height less than 3<sup>rd</sup> percentile which form about 87% of affected patients. This consistent with that in Kitamura M study which concludes that prolonged steroid therapy in frequent relapsing nephrotic syndrome may produce dwarfism and other distressing side effects. (28) In our study we found that there was a very significant relation between growth delay (statural & pubertal) and development of steroid toxicity, were 47(42.7%) of our patients have sign of steroid toxicity in form of cushingoid features with or without hypertension and/or obesity, of them 25(53.2%) have height less than 3<sup>rd</sup> percentile and this form about 80% of affected patients. this consistent with previous studies which suggest that longer steroid treatment with higher cumulative doses of PRD was also the main cause for higher height losses in children with early onset nephrotic syndrome. Foote et al reported that the final adult height of individuals with a history of SSNS is decreased by only 0.22 SD, about 1.5 cm below average height. (30) Several authors have argued that prolonged alternate-day steroid treatment does not impair growth in nephrotic patients. (29, 30) Recovery of the initial channel growth is possible if steroid treatment is discontinued before puberty allowing time for catch-up growth. (30) Patients who are withdrawn from steroids late during childhood may have insufficient time to recover lost height. (30) The use of alternative therapy (alkylating agents; cyclophosphamide or cyclosporine A or others) should be considered, in particular during periods of higher risk for growth retardation.

(15, 16, 18, 28) Loke KY et al study concludes that one year of growth hormone therapy is effective in improving the height standard deviation score, height velocity, bone mineral density, and lean body mass of children with steroid-dependent nephrotic syndrome. There were no significant adverse effects. However, the bone age accelerated at a greater pace than the height age, and further studies are required to define the role of GH therapy in steroid-dependent nephrotic syndrome.<sup>(32)</sup>

**CONCLUSION:**

\* In steroid sensitive nephrotic patients, the prolonged course of the disease with increase number of relapses that expose the patient to more steroid and increase the risk of steroid toxicity, were have a significant rule in delaying the statural growth .

\* Adolescent patients appear to be more affected during puberty.

**RECOMMENDATIONS:**

1. Frequent monitoring of PRD side effects, with switching to alternate day tapering course after remission especially those with frequent relapses.
2. Proper assessment of growth with accurate measurement of height with stadiometer, and weight with scales to gather with charts of height and weight percentiles appropriate for child's age and gender.
3. The use of alternative therapy should be considered, in particular during periods of higher risk for growth retardation.
4. If possible steroid treatment is discontinued before puberty allowing time for catch-up growth.
5. Growth hormone may have a role in affected patients and this need to be studied.

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