Research Article

# Study of the growth and puberty in Iraqi children with nephrotic syndrome

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## Abstract

**Background:** Nephrotic syndrome is a chronic disease with frequent relapses and the accumulative dose of steroid play an important role in developing growth retardation.

**Aims:** To detect the degree of growth retardation in long standing nephrotic syndrome and frequent relapsing nephrotic syndrome, and to identify the effect of nephrotic syndrome and steroid therapy on puberty.

**Patient and methods:** A cross sectional study conducted in Child Central Teaching Hospital from the first of January to first of July 2008, on 108 patients with steroid responding nephrotic syndrome, 60 of them were males and 48 were females. All had anthropometric measurement of height and the assessment depend on Tanner growth centile for age and sex, so as the puberty staging according to Tanner staging. The ranges of the patients ages were 2-17y and the mean age was 11.5±4 y. 59.25% (64) were having steroid toxicity; no patient was on cytotoxic drug.

**Results:** The results were shown that 52/ 108 (48.18%) of the patients have got growth retardation (2SD below the mean) Fifty of the patients were at pubertal age, 30 were males and 20 were females. 39 patients had delayed puberty (78%), 36 patients with delayed puberty had steroid toxicity (94.73%). There is a significant relationship between frequency of relapses, duration of illness and steroid toxicity with incidence of delayed puberty and growth retardation.

**Conclusions:** There is a significant correlation between the growth retardation and the development of steroid toxicity. With frequent relapses and long standing nephrosis, there is a chance to develop growth retardation. Delayed puberty is more with steroid toxicity and it is more in males than females.

**Keywords:** Growth, steroid toxicity, frequent relapses

## INTRODUCTION

Nephrotic syndrome is primarily a pediatric disorder and is 15 times more common in children than adult, with presentation commonly by heavy proteinuria (40 mg/m$^2$/hr in children, or more than 1g/m$^2$/day), hypoalbuminemia (less than 2.5 g/dL), hyperlipidemia, edema.[1-3] The incidence was 2-3/100.000 per year,[4] Most commonly appear between 2-6 year of age,[3] all races are affected,[4] with male affected more than female( 2:1).[1, 4, 5] Children between age of 1-8y are likely to have steroid responsive,[1, 4, 6] prednisolone is used in dose 60mg/m$^2$/day for at least 4 weeks, 80-90% of patients will respond to this treatment, children who continue to have proteinuria (2+ or more) after 8 weeks of steroid treatment are considered steroid resistant.[1, 3]

A relapse is defined as 3-4 ( +) proteinuria plus edema, while frequent relapses considered when relapse equal to four or more times in a 12 months period.[1, 3, 7]

Patient with steroid dependent nephrosis, frequent relapses and steroid resistant nephrosis may develop severe corticosteroid toxicity like Cushingoid appearance, hypertension, cataract, abnormal glucose metabolism, and/or growth failure, also it affects bone maturation center by increasing their maturation and affects final height of patient.[2, 8]

Nephrotic syndrome impairs growth through several mechanisms, the loss of urinary protein and Insulin Like Growth Factor (IGF) binding protein have been cited as a cause for growth failure,[9] also there is significant reduction in (IGF) binding protein – 3 (IGF $BP^3$) and hepatic growth factor mRNA.[10, 11]

In nephrotic syndrome, IGF action on target tissue is inhibited, by competing with type 1 IGF receptor for IGF binding, this alteration is likely to contribute to growth failure in addition to tissue catabolism in nephrotic state.[12]

Nephrotic syndrome as a chronic disease may causes slowing of growth which may or may not be reversible and is often associated with subsequent delay or pubertal failure.[9, 13] In long standing disease process and frequent relapsing state, the cumulative dose of steroid play an important role in developing growth retardation ,where in every year with frequent relapses of nephrotic syndrome there is an increase in chance of developing growth retardation.[12]

Our aim of this study is to assess the growth in long standing nephrotic syndrome and frequent relapsing nephrotic syndrome, and to identify the effect of nephrotic syndrome and steroid therapy on puberty.

## PATIENTS AND METHODS

A cross sectional study was conducted in Childs Central Teaching Hospital for 6 month period from 1st of January to the 1st of July 2008, where 108 patients included in this study.

Full information were taken from each patient including (age, sex, time of diagnosis, duration of the illness, number of relapses per year, compliance with treatment, blood pressure, height, weight, signs of puberty). Blood pressure was measured by sphygmomanometer and appropriate cuff size was used, patient considered hypertensive if blood pressure above 95th percentile.[1]

The height is measured by Harpenedn stadiometer,[14] the accuracy of this method is about $\pm$ ( 0.1-0.3) cm. Standing height is measured by asking the child to stand with straight back with heel firmly touch on the floor, shoulders relax and looking ahead, take breath in and out, whilst gentle upward pressure is exerted upon the mastoid process, the maximum height is then read.

The weight is measured by the same machine, but is excluded from this study because it is found to be not affected due to the disease itself (edema and fluid retention due to the use of steroid). Patients who receive cytotoxic drugs are excluded, to exclude the effects of these drugs on growth.

Puberty is assessed by sexual maturation stage for each sex according to Tanner staging which include in this study breast bud (1st sign of puberty, breast and papilla elevated as small mound, diameter of areola increase) for girls between 8-11 years and testicular enlargement (1st sign of puberty, enlarge pink scrotum, texture altered) for boys between the age 9.5-11 years.

The growth is assessed by mean of height for age and sex according to Tanner growth centile and those who had height more than 2 SD below the mean are considered to have growth retarded. Sign of steroid toxicity which we consider in this study are hypertension and Cushing syndrome. The age 11 years and above is considered pubertal age for girls and 13 years and above for boys, so if girls were above 11 years and boys above 13 years with no sign of puberty considered to be delayed.[1, 15]

Statistical analysis by Chi-square ($X^2$) test to determine the relative importance of various variables. P-value less than or equals to 0.05 was considered as statistically significant.

## RESULTS

Total number of patients included in this study were 108, 60 was males and 48 were females, the ratio of male to female was 1.25:1, as shown in table 1, statistically not significant.

Age range 2-17years, the mean age was 11.5 $\pm$ 4 year, 59.25% of our patients show signs and symptoms of steroid toxicity.

**Table 1.** Distribution of patients and their percentage according to the gender and puberty.

| Gender | No. of patients (%) | Prepubertal (%) | Pubertal (%) |
|---|---|---|---|
| **Male** | 60 (55.55%) | 30 (51.73%) | 30 (60%) |
| **Female** | 48 (44.45%) | 28 (48.27%) | 20 (40%) |
| **Total** | 108 (100%) | 58 (100%) | 50 (100%) |

We find significant relation between growth retardation and steroid toxicity, as shown in table 2.

**Table 2.** The relationship between growth retardation and steroid toxicity.

| Growth (height) | No steroid toxicity (%) | With steroid toxicity (%) | Total (%) |
|---|---|---|---|
| **Retarded** | 60 (55.55%) | 49 (76.56%) | 30 (60%) |
| **No Retarded** | 41 (93.20%) | 28 (48.27%) | 56 (51.85%) |
| **Total** | 44 (100%) | 64 (100%) | 108 (100%) |

$X^2$=50.80 P value=0.002 d.f.=2 Significant relation.

There is a significant relationship between the duration of the disease and growth retardation as shown in table 3.

**Table 3.** The relationship between the duration of disease and growth retardation.

| Growth (height) | Duration < 3y(%) | Duration 3-6y (%) | Duration > 6y (%) | Total (%) |
|---|---|---|---|---|
| **Retarded** | 4 (18.18%) | 30 (51.73%) | 28 (59.57%) | 52 (48.15%) |
| **No retarded** | 18 (81.82%) | 19 (48.72%) | 19 (40.43%) | 56 (51.85%) |
| **Total** | 22 (100%) | 39 (100%) | 47 (100%) | 108 (100%) |

We compare the number of relapses with the growth, we find significant relationship, as increase the number of relapse, will affect the growth, as shown in table 4.

**Table 4.** The relationship between number of relapses and growth retardation.

| Growth (height) | 3 relapse / y (%) | 2 relapse / y (%) | 1 relapse / y (%) | 1relapse /> year (%) | Total (%) |
|---|---|---|---|---|---|
| **Affected** | 23(60.52%) | 19(55.80%) | 8(30.76%) | 2(20%) | 52(48.15%) |
| **Not affected** | 15(39.48%) | 15(44.20%) | 18(69.24%) | 8(80%) | 56(51.85%) |
| **Total** | 38(100%) | 34(100%) | 26(100%) | 10(100%) | 108(100%) |

$X^2$=11.58 P value=0.009 Significant relation

Delay puberty is more in males than females, which was significantly affected as shown in table 5.

**Table 5.** The relationship between delay puberty and gender.

| Gender | Puberty (%) delayed | Puberty (%) Normal | Total (%) |
|---|---|---|---|
| **Male** | 27 (69.23%) | 3 (27.27%) | 30 (60%) |
| **Female** | 12 (30.77%) | 8 (72.73%) | 20 (40%) |
| **Total** | 39 (100%) | 11 (100%) | 50 (100%) |

$X^2$=6.92 P value=0.012 significant

There was a very significant relationship between steroid toxicity and delayed puberty as shown by table 6.

**Table 6.** The relationship between steroid toxicity and delayed puberty.

| Puberty | No steroid toxicity (%) | With steroid toxicity (%) | Total (%) |
|---|---|---|---|
| **Delayed puberty** | 3 (25%) | 36 (94.73%) | 39 (78%) |
| **Normal puberty** | 9 (75%) | 2 (5.27%) | 11 (22%) |
| **Total** | 12 (100%) | 38 (100%) | 50 (100%) |

## DISCUSSION

Since 1955, the standard treatment of nephrotic syndrome is corticosteroid (prednisolone) therapy, 95% of them will respond to steroid and will grow out of childhood nephrotic after puberty, some have 3-5 relapses to occur per year, which may put the child at risk of excessive complications of steroid toxicity, growth impairment is one of these complications.[16]

Our study show a significant relationship between nephrotic syndrome and growth retardation in term of centile of height, this can be seen clearly in cases of frequent relapses per year, where 38 (60.52%) patients with more than 3 relapses per year show growth retardation in comparison with those who have one relapse per more than 1 year, 10 (20%) patients, these results is consistent with other studies like Allen DB and Leonard MB.[16, 17] which shows a significant growth retardation in frequent relapsing nephrotic on steroid and the final height of those patients 2 SD below the means.

Other study showed a significant negative correlation between SDs (standard deviations) and duration of treatment in boys but not in girls, this can be explained by an increase in the incidence of the disease in boys than girls. In the boys height SDs decreased significantly only after the age of 10 y and was associated with delay in appearance of secondary sexual characteristics.[18] KiKuo found that final height in children with steroid sensitive nephrotic syndrome was slightly affected by steroid treatment and two patients from 22 had severe growth retardation.[19]

The development of steroid toxicity in our patients was significant in 59.25% of total patients, and the growth retardation was more in patients with steroid toxicity 76.57% in comparison to 6.8% of 44 patients without steroid toxicity this is similar to the study of Polito C.,[20] which showed a growth retardation and delayed pubertal growth spurt in nephrotic patients receiving alternate day prednisolone but in term of growth velocity and delay growth spurt that was not included in our study, while Saha MT. shows a normal growth of prepubertal nephrotic during long term treatment with repeated courses of prednisolone.[17]

Our study revealed a remarkable degree of delayed puberty, where 50 (78%) patients at pubertal age have a delayed puberty, and the boys more affected than girls, these results are consistent with Allen DB and Alan M., and Rees L et al. which showed growth retardation and delayed puberty in nephrotic patients.[8, 18, 21]

The delayed puberty was more in patients with sign and symptoms of steroid toxicity 38 (94.73%) patients with steroid toxicity this is consistent with Polito C.[20]

The effect of nephrotic on puberty can be contributed to the direct effect of chronic disease, which causes failure of growth and maturation in different ways such as nutritional, metabolic or hormonal.

So we conclude that there is a significant correlation between the growth retardation and the development of steroid toxicity (with alternative day regime), and with frequent relapses and long standing nephrotic there is a chance to develop growth retardation. Delayed puberty is more in patients with steroid toxicity and it is more in males than females.

We recommend, the patients must be carefully followed up not only about apparent side effect of steroid like Cushing syndrome and hypertension but also we must consider growth parameters and assessment of puberty, delayed puberty in nephrotic patients can be considered as a sign of steroid toxicity.

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