Original Research Article

Factors affecting the statural growth retardation in children using steroids in idiopathic nephrotic syndrome

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ABSTRACT

Background and Aim: Idiopathic nephrotic syndrome or nephrosis causes massive protein leakage in the urine. Its treatment requires steroids (prednisone, methylprednisolone), often for a prolonged period, notably in case of steroid-dependence or steroid-resistance. In children, long-term use of steroids can lead to several side effects such as statural growth retardation/ stunting. This study evaluated the frequency of stunting in idiopathic nephrotic syndrome in children on steroids and identified the associated factors.

Material and methods: This was a retrospective, descriptive cohort study carried out in children aged 0 to 16 years treated at the paediatric nephrology unit of Aristide Le Dantec Hospital in Dakar, between 1 December 2017 and 31 May 2020. All records of nephrotic children treated in outpatient or inpatient setting were included. These children had to be on corticosteroid therapy for at least 30 months and have a height taken regularly during follow-up consultations.

Results: Of 259 children followed for idiopathic nephrotic syndrome, 93 were included in the study. The median age was 96.5 months and the sex ratio was 1.9. The mean height of the children at the beginning of the follow-up was -0.26 DS, at the end it was -0.88 DS. At the beginning of the follow-up, 8 children had already stunting. At 12 months follow-up, 72 children (77.4%) had a decrease in z-score; and at 30 months, there were 7 more children (84.9%) who had a decrease in z-score. Methylprednisolone boluses were given to 17 children (18.3%). Calcium supplementation was done in 91 children (97.8%). Vitamin D supplementation was given to 91 children (97.8%). The mean number of relapses was 1.8. Factors associated with stunting were number of relapses ≤3 (p=0.03), duration of corticosteroid therapy >6 months (p<0.0001) and cumulative doses of prednisone >100 mg/kg (p=0.04).

Conclusion: In prolonged nephrotic syndrome in children, corticosteroids can cause stunting

Keywords: Nephrotic syndrome; children; growth; height; steroid, stunting

1. INTRODUCTION

Nephrotic syndrome (NS) in children is defined by the following biological criteria: a hypoproteinemia less than 60 g/l, a hypo-albuminemia less than 30 g/l and a proteinuria greater than 50 mg/kg/24 hours (or proteinuria/creatininuria ratio greater than 2 g/g or 200 mg/mmol) **[1, 2]**. If the NS is prolonged, there is a risk of undernutrition and statural growth retardation due to urinary leakage of proteins including growth hormone, thyroid hormone and vitamin D carrier proteins **[3, 4]**. Idiopathic nephrotic syndrome (INS) or nephrosis is by far the most common cause of nephrotic syndrome in children **[5]**. It is treated worldwide with corticosteroid therapy, carrying the risk of corticosteroid sensitivity, steroid-dependence or steroid-resistance. In the latter two cases, corticosteroid therapy will be prolonged **[2, 6]**. Long-term use of corticosteroids can lead to numerous side effects, such as bone decalcification due to urinary calcium and phosphorus leakage; statural growth retardation due to growth factor inhibition; osteonecrosis due to demineralisation; hypothyroidism due to decreased thyroid secretion and muscle atrophy **[7-9]**.To avoid these side effects, all protocols for the

management of INS recommend adjuvant therapy **[6, 10]**. In different parts of the world, several studies have been conducted on statural growth in children followed for INS with mixed results **[11-13]**. In Senegal, studies have been conducted on childhood INS without mentioning the impact of corticosteroids on their statural growth **[14, 15]**. This evidence gap motivated our work, with the objectives to evaluate the frequency of statural growth retardation in nephrotic children on corticosteroids and to identify associated factors.

2. MATERIAL AND METHODS

2.1 Study design and patient's recruitment

We conducted a retrospective, descriptive cohort study in children aged 0-16 years treated at the paediatric nephrology unit of Aristide Le Dantec Hospital in Dakar (Senegal), between 1 December 2017 and 31 May 2020.

All records of nephrotic children treated in outpatient or inpatient setting during the study period were included. These children had to be on corticosteroid therapy (prednisone) for at least 12 months, and at most 30 months, and have a regular height taken at follow-up visits.

Not included were children who had changed follow-up location or whose records were incomplete, and nephrotic children in chronic renal failure (CRF).

2.2 Data collection and definition of operational variables

The files were analysed using a data collection form with several parameters:

- ✓ Socio-demographic data: age at diagnosis, gender.
- ✓ Anamnestic data: length of follow-up, number of relapses.
- ✓ Diagnostic data: height of children, measurements and paraclinical examinations.

- Measurements: only the height was taken into account. Height, expressed in centimetres, was taken every 6 months. It was related to age and the height-for-age z-score was expressed as standard deviation (SD z-score = (measure - mean) / standard deviation of the reference population.)

Our reference population was the 2007 World Health Organization (WHO) population **[16]**. Any loss of points from the baseline z-score was defined as stunting. This stunting was assessed statically or dynamically. The stunting was defined statically as a z-score below -2 SD. Dynamically, this stunting was defined as a decrease in statural growth of more than 1.5 SD during follow-up **[17]**. Height decrement was defined as a slowing down and/or retardation of statural growth.

- Paraclinical examinations: proteinemia, albuminemia, 24-hour proteinuria to define relapses; and bone densitometry.

- ✓ Therapeutic data: duration of corticosteroid therapy, type of idiopathic nephrotic syndrome, threshold and number of relapses, use of immunosuppressants, calcium and vitamin D supplementation, sodium restriction, methylprednisolone boluses and cumulative corticosteroid doses (mg/kg). The latter was obtained by multiplying the duration of treatment (number of days) by the dosage of Prednisone (mg/kg/day).

2.3 Data collection and statistical analysis

The data collected was entered into Excel 2016 and analysed using RStudio 1.3.1093. Quantitative variables were presented either as means or medians with their ranges or as proportions. The Fisher test was carried out to define correlation with a significance threshold for a p-value (p) of less than 0.05.

3. RESULTS

Of 259 children followed for idiopathic nephrotic syndrome, 93 were included in the study. The median age was 96.5 months [15; 192 months]. The age range [60; 144 months[was the most common **(figure 1)**.

The sex ratio (m/f) was 1.9. The mean height for age z-score of the children at the beginning of the follow-up was 0.26 SD [-3.42; 2.53 SD]. Thereafter, it decreased progressively and was -0.57 SD [-3.7; 1.88 SD] at 12 months and -0.88 SD [-3.6; 1.57 SD] at 30 months **(figure 2)**. However, at the beginning of the follow-up, 8 children (8.6%) had already stunting.

At 12 months follow-up, 72 children (77.4%) had a decrease in z-score; and at 30 months, there were 7 more children (84.9%) who had a decrease in z-score. Bone densitometry was performed in 3 children who all showed femoral and lumbar bone demineralisation. Methylprednisolone boluses were performed in 17 children (18.3%). In our study, 3 immunosuppressants were used in 18 children, including mycophenolate mofetil (MMF) in half of the cases (n=9). Immunosuppressants were combined with corticosteroids. Calcium supplementation was performed in 91 children (97.8%). Vitamin D supplementation was given to 91 children (97.8%). The average dose of vitamin D given was 511.5 IU/d [125; 800 IU/d]. Sodium restriction was performed in 91 children (97.8%). The children included in the study were either steroid-dependent (90.3%) or steroid-resistant (9.7%). The mean number of relapses was 1.8 [1; 7 relapses]. The mean threshold for relapse was 0.43 mg/kg/day [0.1; 1.5 mg/kg/day]. Factors associated with stunting **(table I)** were number of relapses ≤3 (p=0.03), duration of corticosteroid therapy > 6 months (p< 0.0001) and cumulative prednisone doses > 100 mg/kg (p=0.04).

4. DISCUSSION

Corticosteroid therapy inhibits statural growth, but reversibly if the corticosteroid is stopped before bone growth is complete **[18]**. Moreover, the acquisition of peak bone mass is mainly achieved during prepuberty and puberty. Prolonged exposure to glucocorticoids during these periods can lead to permanent statural growth retardation **[19]**. In our study, more than half of the children (66.7%) were between 49 and 144 months of age, while less than a quarter (15.0%) were older than 144 months. These results are similar to those found by Coulibaly et al. in Ivory Coast, with 66.6% of children between 48 and 144 months of age and 10.0% over 144 months **[20]**. At the start of corticosteroid therapy, some children (8.6%) had already stunting and this was accentuated during follow-up. This delay could be explained by massive and persistent proteinuria before the start of corticosteroid therapy or by other factors such as nutrition. The statural growth retardation experienced by children with NIS is thought to be due, on the one hand, to the effects of steroid therapy on height **[9]**, on the other hand, tp the urinary leakage of proteins, including certain hormones (growth hormone, insulin growth factor-1 or IGF1 and proteins carrying thyroid hormones or vitamin D). **[3, 4, 21]**. Although the children were put on long-term corticosteroids (30 months), only 3 children had been able to have a bone densitometry. This showed diffuse femoral and lumbar bone demineralisation in all cases. Bone density measurement allows monitoring the impact of glucocorticoids on bone remodelling and destruction. It is useful when corticosteroid-sparing therapy is being considered when there are clinical symptoms suggestive of bone complications **[9]**, but these drugs are often inaccessible in developing countries. The mean cumulative dose of corticosteroids was 456.9 mg/kg. In other studies, this dose varied from 452.6 to 2205.9 mg/kg. The differences found in these studies are thought to be related to the duration of steroid therapy **[11, 12, 22, 23]**. Corticosteroid-sparing immunosuppressive treatment is indicated in cases of steroid-dependent or steroid-resistant nephrotic syndrome. It avoids signs of steroid intolerance **[2, 3]**. The relatively high cost of immunosuppressive drugs and sometimes their unavailability explain their low use in these children despite the indications. In childhood INS, the systematic administration of 600-800 IU of native vitamin D per day is recommended, with the aim of achieving a 25-OH vitamin D3 level of >30 ng/ml **[2]**. Calcium supplementation is also recommended to keep intakes slightly above the recommended daily dosis **[2, 17]**. In our study, 91 children (97.8%) received vitamin D3 and calcium supplementation, whereas in the study by Coulibaly et al. only 14 children (46.7%) received this supplementation **[20]**. The mean number of relapses was 1.8 with a mean corticosteroid threshold at the time of relapse of 0.43 mg/kg/day. This threshold is higher than the one at which secondary effects on bone

density and height occur (0.16 mg/kg/d prednisone) **[24]**. The PNDS (Protocole National de Diagnostic et de Soins) on nephrotic syndrome in children proposes different treatment durations for relapses, depending on their time of onset, but generally treatment duration of subsequent relapses is longer than for a first relapse **[2]**. The risk of statural growth retardation increases due to prolonged exposure to corticosteroids **[9]**. Factors associated with statural growth retardation were number of relapses ≤3 ($p=0.03$), duration of corticosteroid therapy > 6 months ($p<0.0001$) and cumulative corticosteroid doses > 100 mg/kg ($p=0.04$). These factors are inter-related. At 6 months of corticosteroid therapy (prednisone), the height for age of nephrotic children already started to decrease ($p<0.0001$). The decrease in height for age z-score of the nephrotic children, which was predominant during the first months of follow-up, is due to the action of corticoids, which promote bone resorption **[25]**. This action of corticosteroids is maximal at the beginning of the treatment and will tend to decrease with time **[25]**. Our results were in line with those of most studies on the action of corticoids on statural growth in children **[11, 23, 26, 27]**, with a decrease in children height that is more linear **(figure 2)**. However, an Ivorian study found a contradiction with a gain in z-score during the follow-up of nephrotic children **[20]**. Long-term corticosteroids lead to a decrease in bone formation through a direct pro-apoptotic action of corticosteroids, a modification of the mode of secretion of PTH, a decrease in the action of IGF1, growth hormone and androgens **[25]**. The limitations of our study were the inability to measure vitamin D and to perform bone densitometry in all children, due to our sample size and the retrospective nature of our study. Hence the need for a prospective study to better substantiate these results.

5. CONCLUSION

In our study, statural growth retardation was more important during the first year of follow-up. The factors associated with the decrease in height of the children were the number of relapses, the duration of corticosteroid therapy and the cumulative doses of corticosteroids. Monitoring the statural growth of nephrotic children becomes an obsession in the case of prolonged corticosteroid therapy.

ETHICAL APPROVAL

This study was conducted in accordance with the Declaration of Helsinki. To respect the confidentiality, an identification code was assigned to each patient. This study was a hospital-based research conducted in routine conditions.

Consent

Written informed consent was from patients

DISCLAIMER

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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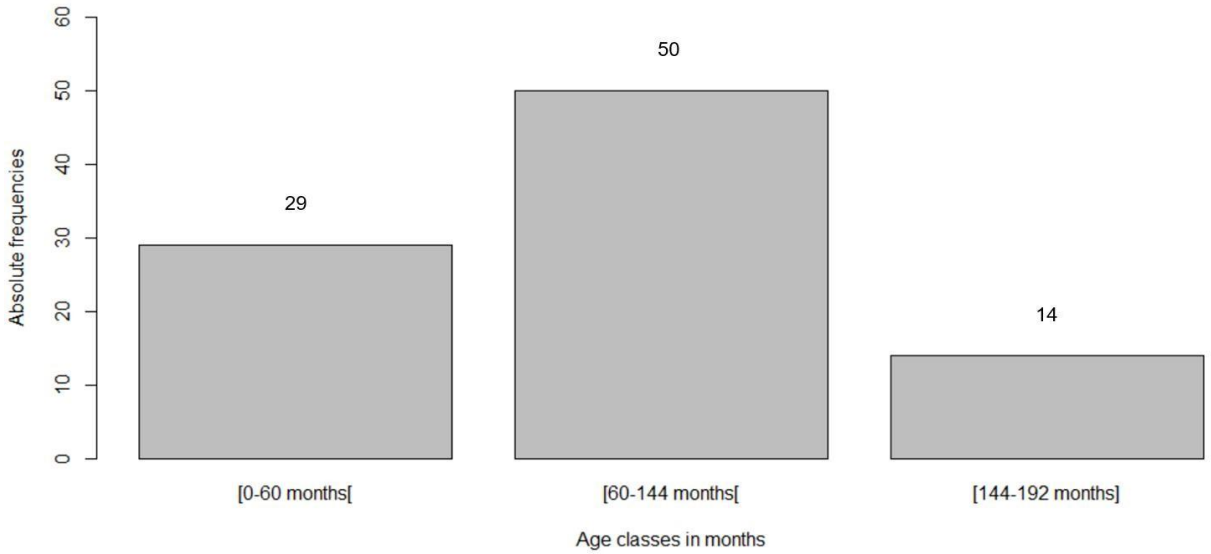

Figure 1: Distribution of children by age group

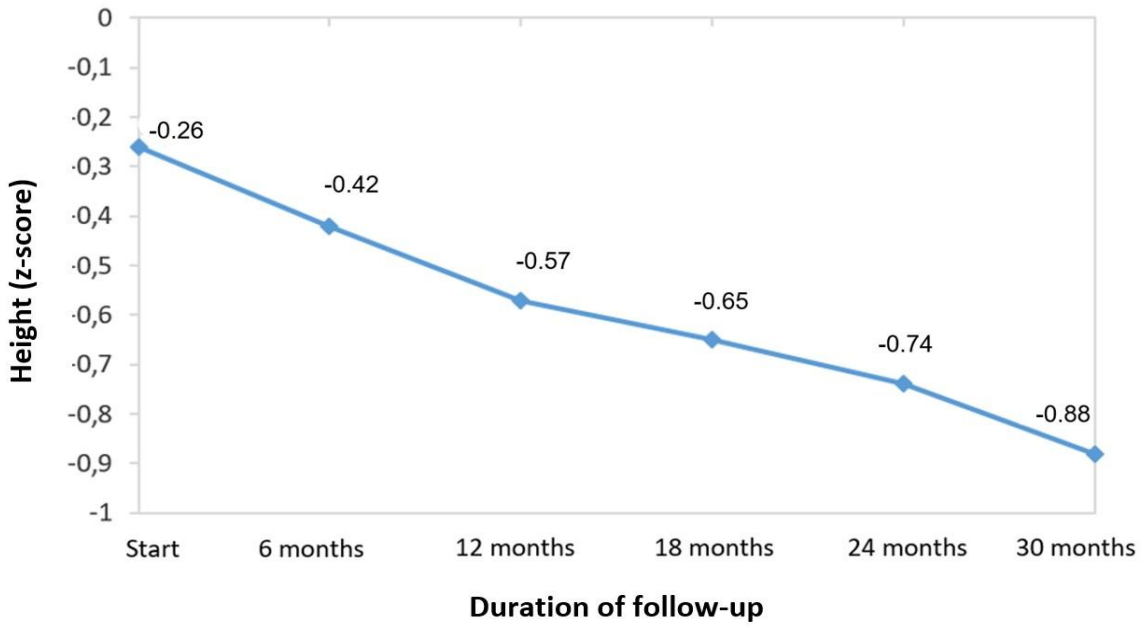

Figure 2: Changes in median height of children during follow-up

Table I: Factors associated with statural growth retardation in children with idiopathic nephrotic syndrome

Factors	Decrease in statural growth (z-score)		p-value
	No n (%)	Yes n (%)	
Age			
≤10 years	16 (23.9)	51 (76.1)	0.57
> 10 years	4 (15.4)	22 (84.6)	
Type			
Male	12 (19.7)	49 (80.3)	0.60
Female	8 (25.0)	24 (75.0)	
Number of relapses			
≤ 3	20 (29.0)	49 (71.0)	**0.03***
> 3	0 (0.0)	13 (100.0)	
Duration of steroid therapy			
≤ 6 months	11 (73.3)	4 (26.7)	**< 0.0001***
> 6 months	9 (11.5)	69 (88.5)	
Cumulative doses of Prednisone			
≤ 100 mg/kg	2 (100.0)	0 (0.0)	**0.04***
> 100 mg/kg	18 (19.8)	73 (80.2)	
Vitamin D3 supplementation			
≤ 400 IU/day	9 (16.7)	45 (83.3)	0.21
> 400 IU/day	11 (28.2)	28 (71.8)	

*: significant p-value (< 0.05); **IU**: international unit; **mg**: milligram; **kg**: kilogram