Pediatr Nephrol (1994) 8: 480–482
© IPNA 1994

Pediatric Nephrology

Brief report

Alternate-day steroids affect carpal maturation more than radius, ulna and short bones

Cesare Polito[1], Nicola Greco[2], Antonio Opallo[1], Ersilia Cimmaruta[1], and Angela La Manna[1]

[1]Department of Paediatrics, 3rd Paediatric Clinic and [2]Radiological Sciences Institute, Second University of Naples, Naples, Italy

Received June 30, 1993; received in revised form and accepted February 9, 1994

Abstract. Radius, ulna, short bones (RUS) and carpal (CARP) bone age were assessed in 26 steroid-dependent nephrotic boys after at least 1 year of alternate-day prednisone therapy, and in 26 age- and sex-matched control subjects. No significant difference in RUS bone age was found between patients and controls. CARP bone age of patients was significantly ($P = 0.01$) more retarded than in controls. In patients, CARP bone age delay was related to their relative height at the time of study ($P = 0.01$). We conclude that CARP bones are more prone to effects of steroids than are RUS bones. Therefore, CARP bone age may be a more sensitive tool in monitoring the effects of steroids on skeletal growth and maturation.

Key words: Skeletal maturity – Steroids – Nephrotic syndrome

Introduction

The assessment of bone age is used to evaluate growth potential, predict adult height and monitor the effects of therapy in children with growth retardation. It is well known that steroids can retard statural growth as well as bone age [1–4]. Tanner et al. [5] developed a method to determine bone age using the radius, ulna, short bones (RUS) and the carpal (CARP) bones. Relatively little is known about RUS-CARP differences, either in healthy children or in disease states. Tanner et al. [5] reported that in 2- to 13-year-old boys and 2- to 11-year-old girls the mean difference between the two scores is zero. Hence, the RUS/CARP ratio should be approximately 1.0 within these age ranges. By the time youngsters approach puberty (roughly 13 years for boys and 11 years for girls) the CARP score is at the 97th percentile and can progress no further. These authors [5] hypothesized that the RUS/CARP ratio may be affected by endocrine derangements, but no data are available on this subject.

Cundall et al. [6] recently reported a retarded CARP bone age compared with RUS bone age in children with chronic renal failure. Some of their patients were receiving steroids, but there were too few to study steroidal effects. Here we report RUS and CARP bone age in boys with steroid-dependent nephrotic syndrome (SDNS) who received alternate-day prednisone (PDN) for at least 1 year.

Patients and methods

We studied the left hand radiographs from 26 Caucasian boys with SDNS (age range 3.8–12.9 years) and a control group of 26 age-matched normal boys. The patients received 0.3–1.9 (mean 0.8) mg/kg body weight of PDN on alternate days in two divided doses with vitamin D and calcium, for 1–7.5 years (mean 2.6 years).

Short-term (maximum 13 days) daily PDN was given during disease relapses. The total amount of PDN taken ranged from 0.4 to 42.7 g (mean 11.5 g).

The controls had left hand radiographs taken to predict adult height before starting sports. RUS and CARP bone ages [5] were assessed by one of us (A.O.) and the RUS/CARP bone age ratio calculated. The bone age delay was determined as the difference between chronological age and bone age. Radiographs from 10 patients and 10 controls were blindly reassessed after 3–6 months. The reliability of assessment was expressed as the mean and standard deviation of the differences between the first and second assessment and also as the technical error in measurements [7] calculated using the following

$$\text{formula: technical error of measurement} = \sqrt{\frac{\sum d^2 1,2}{2\,n}}$$

where d 1,2 are the differences between the first and second assessment and n is the number of radiographs assessed. The mean difference between the first and the second assessment was 0.25 ± 0.63 years for RUS and 0.16 ± 0.60 years for CARP bone ages. The technical error in measurement was 0.46 years for RUS and 0.40 for CARP bone ages. These results indicate good repeatibility of one observer's bone age estimations [6, 7].

Stature was measured by a Harpenden stadiometer. To analyse the deviation from normal values, the heights were converted to height

Correspondence to: C. Polito, Clinica Pediatrica III, Via S. Andrea delle Dame 4, 80138 Napoli, Italy

Table 1. Data from 26 steroid-dependent nephrotic boys and from 26 sex- and age-matched controls

		Patients		Control group	
Chronological age (years)		8.4 ± 2.6 (3.8 to 12.9)		8.4 ± 2.6 (3.7 to 13)	
RUS bone age (years)		8.4 ± 2.5 (4 to 12.5)		8.22 ± 2.7 (2.8 to 14.5)	
	$r = 0.6$, $P = 0.001$		z = 2.67, $P = 0.008$		$r = 0.42$, $P = 0.03$
CARP bone age (years)		7.1 ± 2.0 (4.7 to 11.4)	⟷	8.02 ± 2.4 (2.8 to 1.4)	
			z = 2.59, $P = 0.01$		
CARP bone age delay (years)		1.3 ± 1.4 (–0.9 to 4)	⟷	0.35 ± 1.01 (–1.8 to 2.3)	
			z = 3.24, $P = 0.001$		
RUS/CARP ratio	$r = -0.5$, $P = 0.01$	1.2 ± 0.2 (0.7 to 1.6)	⟷	1.02 ± 0.07 (0.93 to 1.15)	
HSDS last visit		–0.27 ± 1.1 (–2.76 to 1.34)		0.07 ± 0.73 (–1.53 to 1.54)	

RUS, Radius, ulna, short bones; CARP, carpal; HSDS, height standard deviation score

[a] Comparison of data from patients and controls as well as data within a group have been made. Only significant differences (*horizontal lines*) and correlations (*vertical lines*) are reported. Values are expressed as mean ± SD and (range)

standard deviation score (HSDS) according to Tanner and Whitehouse standards [8]. These were similar to those obtained in normal children from our region [9]. The overall amounts of PDN and the average daily PDN dose that each patient received during therapy were calculated.

The difference between mean values was studied by the Wilcoxon test; any correlation between two series of values was assessed by the Spearman test. *P* values below 0.05 were considered significant.

Results

The results are reported in Table 1. The mean stature of patients at the start of therapy was 0.03 ± 0.9 HSDS and –0.27 ± 1.1 at the time of bone age evaluation. The mean loss of relative height during therapy was –0.11 HSDS/year. Stature at the time of study was not significantly different from that of controls (Table 1). In patients the RUS bone age was no different from chronological age, so that the RUS bone age delay was irrelevant (–0.09 ± 0.9 years). No difference was found between the RUS bone age of patients and controls. In contrast, the CARP bone age of patients was significantly lower and the RUS/CARP ratio was significantly higher than in controls. There was a positive correlation between CARP bone age delay of patients and their chronological age (Table 1). This was also true ($r = 0.52$, $P = 0.016$) when considering the 22 patients less than 11 years. In the control group as a whole, the correlation of CARP bone age delay and chronological age was less significant (Table 1). A significant inverse correlation was also found between CARP bone age delay and HSDS in patients but not in controls. No relation was found between CARP bone age delay and duration of therapy, total PDN amounts and average daily PDN administered per kilogram body weight.

We have longitudinal data in only 8 patients and none of them had radiographs taken at the start of therapy. In 6 subjects the RUS/CARP ratio did lag to 1.1–1.5 with continuing therapy. In 2 patients, the RUS/CARP ratio was 1.6 and 1.34 after 2 and 3 years of therapy and dropped to 1.08 and to 1, respectively 1 year after the withdrawal of steroids.

Discussion

The present study was designed to assess the effect of alternate-day PDN on carpal maturation in children with SDNS. Steroids are administered in various chronic childhood diseases but it is very difficult to differentiate the effects of steroids on bone maturation from those due to disease itself.

There is no evidence that SDNS, in the presence of normal glomerular filtration rate and periods of short-lasting proteinuria, affects carpal maturation. However, it is reasonable to assume that the effects of SDNS on carpal maturation are minimal – if any. Indeed, urinary loss of proteins and of calcium and hormones bound to the proteins lasts for no longer than a few days in SDNS, because effective steroid therapy is rapidly given. Therefore, SDNS represents one of the best available models to study the effects of alternate-day steroids on skeletal maturation in humans.

The main finding of our study is retardation of CARP bone age after long-term alternate-day PDN therapy, in the

face of normal RUS bone age. This suggests that carpal bones are more prone than the radius, ulna and short bones to the effects of steroids. This finding is even more striking when considering that it is drawn from a population of patients whose statural growth is little affected by steroid therapy. Our patients lost only 0.11 HSDS/year during therapy, and their stature during the study was not significantly different from controls. It is well known that alternate-day PDN has little effect on the statural growth and bone (RUS) maturation of pre-pubertal SDNS patients [4, 10]. PDN mostly affects statural growth and bone maturation during puberty [3, 4]. It is likely that the CARP bone age would be even more retarded in subjects treated with daily steroids or with alternate-day steroids in higher doses than those taken by our patients.

It is noteworthy that CARP bone age delay was inversely related to statural growth performance. Therefore, the retardation of CARP bone age was not only very sensitive to alternate-day PDN, but also appeared linked to even minimal slow-down in linear growth.

In our patients CARP bone age delay significantly rose with age, but was neither related to amounts of PDN taken nor to duration of therapy. This age-related delay cannot be attributed to puberty, because we found a significant relation between chronological age and CARP bone age delay even after excluding the patients greater than 11 years old. Steroids may magnify the already increasing CARP bone age delay with chronological age that we saw to a lesser extent in control subjects.

Our longitudinal data are still too limited for accurate statistical analysis. Some logically expected correlations (i.e. between CARP bone age delay and the amounts of PDN taken or the duration of therapy) did not reach significance in our sample. Longitudinal studies on a larger scale are needed if these findings are to be confirmed. This should be of interest, because the high sensitivity of CARP bone age to steroids and its relation to even minimal statural growth slow-down may give us a more useful tool to monitor the effects of steroids on skeletal growth and maturation.

References

1. Byron MA, Jackson J, Ansell BM (1983) Effect of different corticosteroids on hypothalamic-pituitary-adrenal axis and growth in juvenile chronic arthritis. J R Soc Med 76: 452–457
2. Kerrebjin KF, De Kroon JPM (1968) Effect on height of corticosteroid therapy in asthmatic children. Arch Dis Child 43: 556–561
3. Rees L, Greene JA, Adlard P, Jones J, Haycock GB, Rigden SPA, Preece M, Chantler C (1988) Growth and endocrine function in steroid-sensitive nephrotic syndrome. Arch Dis Child 63: 484–490
4. Polito C, Di Toro R (1992) Delayed pubertal growth spurt in glomerulopathic boys receiving alternate-day prednisone. Child Nephrol Urol 12: 202–207
5. Tanner JM, Whitehouse RH, Marshall WA, Healey MJR, Goldstein H (1975) Assessment of skeketal maturity and prediction of adult height (TW2 method). Academic Press, London
6. Cundall DB, Brocklebank JT, Buckler JMH (1988) Which bone age in chronic renal insufficiency and end-stage renal disease? Pediatr Nephrol 2: 200–204
7. Cameron N (1984) Measurement of human growth. Croom Helm, Beckenham
8. Tanner JM, Whitehouse RH (1976) Clinical longitudinal standards for height, weight, height velocity, weight velocity and stage of puberty. Arch Dis Child 51: 170–179
9. Greco L, Mayer M, Grimaldi M, Capasso G (1982) Factors affecting growth in Campania's schoolchildren. Acta Med Auxol 14: 177–187
10. Polito C, Oporto MR, Totino SF, La Manna A, Di Toro R (1986) Normal growth of nephrotic children during long-term prednisone therapy. Acta Paediatr Scand 75: 245–250

Literature abstract

Clin Nephrol (1993) 40: 308–314

Reflux nephropathy in children submitted to unilateral nephrectomy: a clinicopathological study

R. A. Risdon, C. K. Yeung, and P. G. Ransley

The clinical findings and renal histopathology have been reviewed in children with gross primary vesicoureteric reflux (VUR) submitted to unilateral nephrectomy. Of the 42 children reviewed, sections of the nephrectomy specimens were available in 36. In this series, 34 patients were male and eight were female. The boys included seven in which hydronephrosis was identified by fetal ultrasound. The male patients tended to present earlier and had nephrectomies younger than the females. Segmental scarring was frequent in both males and females, but evidence of dysplastic renal development was confined to the male patients and occurred in the majority (63%). Acquired mechanisms for the induction of segmental renal scarring, involving VUR, intrarenal reflux (IRR) and urinary infection, shown to be important in older children, clearly operate in infancy. However, this study emphasizes that congenital malformation of the kidney is a crucial factor in the development of reflux nephropathy (RN) in this younger age group, particularly in males. Speculation on the significance of the association between renal dysplasia and RN is discussed in relation to observations on the embryological development of the male lower urinary tract.