Assessment of serum prostate specific antigen in childhood

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OBJECTIVE

To investigate serum prostate specific antigen (PSA) levels with age and sex in childhood.

SUBJECTS AND METHODS

This prospective study included 205 children (123 boys, 82 girls; mean age 59.27 months, SD 3.78, range 2 days to 204 months) with no urogenital or endocrine disorders. PSA levels were measured using a highly sensitive, 'third-generation' PSA (time-resolved immunofluorometric) assay, able to detect PSA levels of ≥1 ng/L (0.001 ng/mL). Children were divided into four groups by age, i.e. A (0–12 months; 34 boys/20 girls); B (13–48, 37/21); C (49–144, 41/32); and D (> 144, 11/9). The data were analysed statistically using analysis of variance.

RESULTS

An accurate measurement of PSA was possible in both sexes using the assay. The median (SD, range) PSA level in boys was 38.41 (1.318, 1–2768) ng/L, and in girls 4.059 (1.392, 1–287) ng/L. There were no significant differences between girls at all age groups, or between the sexes for groups A–C, but levels were significantly higher in boys in group D (30 times that in girls), at 142.59 (1.53) and 4.85 (1.58) ng/L ($P < 0.01$).

CONCLUSIONS

PSA levels do not differ significantly between boys and girls until 12 years old, after which there is a significant and steep increase in PSA in boys, reflecting the development of the prostate. Assessing PSA in children could be used as a potential marker in the diagnosis and follow-up of urogenital disorders.

KEYWORDS

prostate specific antigen, PSA, childhood, urogenital disease

INTRODUCTION

PSA is a single-chain glycoprotein, consisting of 237 amino acids with a molecular weight of 33 kDa, produced in the endoplasmic reticulum of prostatic epithelial cells. The gene coding PSA lies on the long arm of chromosome 19 between the 19q13.2 and 19q13.4 loci [1–3]. PSA is a serine protease and an esterase, with both chymotrypsin-like and trypsin-like activity. From its action, its polypeptide structure and location of its gene, PSA is considered to be a member of the kallikrein family, and the gene which decodes it is characterized as *HKLK3* (human kallikrein 3) [4]. PSA is found in high concentrations in the seminal fluid (up to 5 mg/mL, i.e. 1000 times its normal concentration in serum) [4,5]. Its production depends mainly on androgens, and recently it has been detected in the serum of young males and females [5,6].

The clinical importance of PSA as a biochemical tumour marker in the diagnosis and follow-up of the course of prostatic adenocarcinoma has led to the development of highly sensitive methods for its detection [7]. By using these methods it is possible to detect very low serum PSA levels, and this is particularly important in cases where PSA levels are substantially lower than those determined by the conventional methods in use (≥20 ng/L or 0.02 ng/mL).

We hypothesized that PSA levels could be used as a marker in the diagnosis and follow-up of urogenital disease in children, and thus we determined its normal levels in children with no urogenital or endocrine disorders, using a new highly sensitive assay developed in our laboratory (by E.D.). Thus the purpose of this study was: (i) to determine whether PSA can be detected in the serum of healthy children aged 0–14 years and to determine its limits; (ii) to determine if there are any significant differences in PSA levels between the sexes or with age groups from 0 to 14 years.

SUBJECTS AND METHODS

The prospective study included 205 children (123 boys and 82 girls; mean age 59.27 months, SD 3.78, range 2 days to 204 months) after obtaining parental informed consent. The children had no urogenital or endocrine disorders, took no hormonal medication and had a normal temperature at the time of the investigation. Blood samples (5 mL) were taken in the morning (between 08.00 and 09.00 hours), centrifuged for 5 min, and the sera immediately refrigerated and kept at –30 °C until analysis.

PSA levels in the serum were measured using a highly sensitive, third-generation PSA (time-resolved immunofluorometric) assay, based on two monoclonal antibodies reacting with the enzyme. The method was fully described previously [7] and can detect PSA levels of ≥1 ng/L (0.001 ng/mL).

Children were divided into four groups according to age: A (0–12 months), B (13–48), C (49–144) and D (>144). The collected data were analysed statistically using an ANOVA model, which allows an assessment of the significance of differences between the mean values of more than two variables using the

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TABLE 1 Mean PSA values by age and gender

	PSA, mean (range) [CI], ng/L	
Age group	Boys	Girls
A	4.711 (4.288–5.135) [4.361–5.090]	5.754 (5.163–6.346) [5.062–6.542]
B	2.915 (2.514–3.317) [2.713–3.133]	3.199 (2.613–3.77) [2.814–3.616]
C	3.421 (3.043–3.799 [3.206–3.651]	2.435 (1.99–2.88) [2.236–2.652]
D	142.6 (141.7–143.5) [109.2–186.1]	4.855 (3.82–5.89) [3.595–6.563]

linear model: log PSA = $B_0 + B_1 \times A + B_2 \times D + B_3 \times \text{boys} \times D$

where B_0 represents a constant (1.093), B_1 the coefficient of variance of sex (0.503), B_2 the coefficient of variance of age group (0.488), B_3 the coefficient of interaction between the coefficients of variance of sex and age groups (3.379), and A and D represent the number of children in the corresponding age groups.

The mean values of PSA in each group were determined as

$(X \pm 1.96) \times \text{SEM}/\sqrt{n}$

Where X represents the mean value for the age and sex group, 1.96 is a constant corresponding to the normal distribution of the sample, SEM is the standard error for the age and sex group, and *n* is the sample number for the age and sex group.

RESULTS

PSA was detected in the children of both sexes, with a median (SD, range) in boys of 38.41 (1.311, 1–2768) ng/L and in girls of 4.059 (1.392, 1–287) ng/L. PSA levels did not differ significantly among the age groups A–C (Table 1), nor between boys and girls until 12 years old, after which there was a significant and steep increase in PSA in boys, most probably reflecting the development of the prostate gland. PSA levels of boys in group D were 30 times those of the corresponding girls ($P < 0.01$), this being the only significant difference detected among the four age groups in both sexes.

DISCUSSION

PSA has been used as a biochemical marker in the diagnosis and follow-up of patients with prostate cancer. The follow-up of PSA levels in patients after radical prostatectomy is particularly important, as serial biochemical findings allow the timely detection of local disease recurrence or distant metastases.

That the prostate gland is not the only source of PSA, and the possibility of measuring very low PSA levels in serum, offer new possibilities for its more extended use as a biological marker [8]. In children, PSA is produced by male and female periurethral glands, and by rectal glands [8,9]. The anatomical organization of periurethral glands to form a prostate gland has been histologically confirmed in male neonates, and the histological appearance of female periurethral glands is similar to that of the immature prostate before adolescence, although these glands do not develop further because of the lack of androgenic stimulation [10,11]. Periurethral glands in females are considered to be primarily responsible for secreting PSA, as shown by immunohistochemical findings [12].

In the present study we showed that it is possible to detect PSA in both boys and girls aged <14 years. The highly sensitive assay accurately measured normal PSA levels with age and sex. PSA does not differ between boys and girls up to the age of 12 years. The significant increase of PSA in boys after this age most probably reflects the increase in prostate gland volume caused by androgenic stimulation. The change in prostate gland volume during adolescence had been empirically supported for years by the clinical observation of boys with urinary incontinence resulting from urethral sphincter failure (e.g. reconstructed epispadias) who spontaneously improve with the onset of adolescence.

The practical implication of defining the distribution of normal PSA values in healthy children lies in the assumption that PSA may also be used as a potential biochemical marker in assessing children with various urogenital disorders. PSA has been measured in boys to monitor the progress of normal [13] or precocious [14] puberty. A further potential application of PSA measurement could be in prepubertal boys with micropenis or microphallic hypospadias, in whom treatment with testosterone is considered. Basic levels of PSA before treatment could serve to indicate the quality of their androgen receptors and hence as a predictor of their clinical response to testosterone treatment, i.e. of their penile length, which is the question most often asked by the parents of such patients. Furthermore, PSA measurements could be used in both boys and girls with neuropathic and non-neuropathic voiding dysfunction, as a biochemical marker in following the course of their disease. In such cases the existing chronic and recurrent urethritis could theoretically result in the destruction of periurethral glands, liberating PSA into the systemic circulation and increasing PSA levels. Conversely, effective therapeutic measures would result in decreasing the PSA level. Indeed, such a study investigating the changes of PSA in the serum and urine of children with dysfunctional voiding is currently underway in our department.

In summary, PSA levels do not differ significantly between boys and girls until 12 years old, after which there is a steep increase of PSA in boys. Changes in PSA could be useful as a biochemical marker in the diagnostic evaluation and follow-up of children with urogenital disorders.

CONFLICT OF INTEREST

None declared.

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