Male gonadal function before and after chemotherapy in prepubertal boys

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Abstract

We evaluated gonadal function in twenty prepubertal boys (6.87 ± 3.84 years old) at diagnosis and 2.5 ± 1.6 years after treatment for acute lymphoblastic leukaemia (ALL). We measured serum levels of inhibin B (RIA method), testosterone, FSH, LH (immunoenzymatic methods) and compared the results with controls (31 healthy boys in prepubertal stage). Results: Serum inhibin B levels were lower at diagnosis (55.81 ng/ml ± 33.74), comparing to respective values in the controls (105.89 ng/ml ± 46.64), $p<0.0002$. The values of inhibin B slightly augmented after 2.5 ± 1.6 years from chemotherapy (79.47ng/ml ± 47.39), $p<0.06$ but remained lower than those in the controls ($p<0.07$). We did not find any differences in FSH, LH or testosterone values, before and after chemotherapy, comparing to respective values in the controls. In conclusion, haematological malignancy and its treatment influence gonadal function before puberty with a possibility of recovery. During this period, inhibin B could be used as a sensitive indicator of testicular function.

Key words: acute lymphoblastic leukaemia, late effects, male infertility, children, inhibin B.

Introduction

Endocrine abnormalities are a common late effect of anticancer treatment, both in children and adults, including pituitary, thyroid and gonadal dysfunction [1]. Male gonads have two important functions: spermatogenesis and steroidogenesis. The production of testosterone and 17 b-estradiol by Leydig cells is under control of the hypothalamus and the pituitary gland (LH, luteinizing hormone). Follicle stimulating hormone (FSH) influences Sertoli cells to stimulate the release of a protein - inhibin B - which exerts a negative feedback of FSH secretion [2].

Gonadal damage, induced by neoplastic process per se or by chemotherapy and/or radiotherapy, affects both components of gonadal function, resulting in infertility and sexual dysfunction, which may compromise the quality of life of the survivors [1].

We do not have an unambiguous opinion if the testicular injury after anticancer treatment in boys is similar in prepubertal and pubertal stage. In this study, we evaluated the gonadal function in prepubertal boys, treated for acute lymphoblastic leukaemia (ALL).

Patients and methods

Twenty boys, at the mean age of 6.87 ± 3.84 years (at diagnosis), in Tanner stage I or II, were studied before and 2.5 ± 1.63 years after the treatment for ALL, according to BFM 90 protocol. Thirty-one healthy boys in a similar age (6.87 ± 2.41years old) were examined as controls.

We determined serum concentrations of inhibin B (radioimmunoassay method) and FSH, LH and testosterone (immunoenzymatic methods).

The study was approved by the local ethics committee.

Results

Serum inhibin B levels were lower at diagnosis (55.81 ng/ml ± 33.74), in comparison to the results, obtained in the control group (105.89 ng/ml ± 46.64), $p<0.0002$. After

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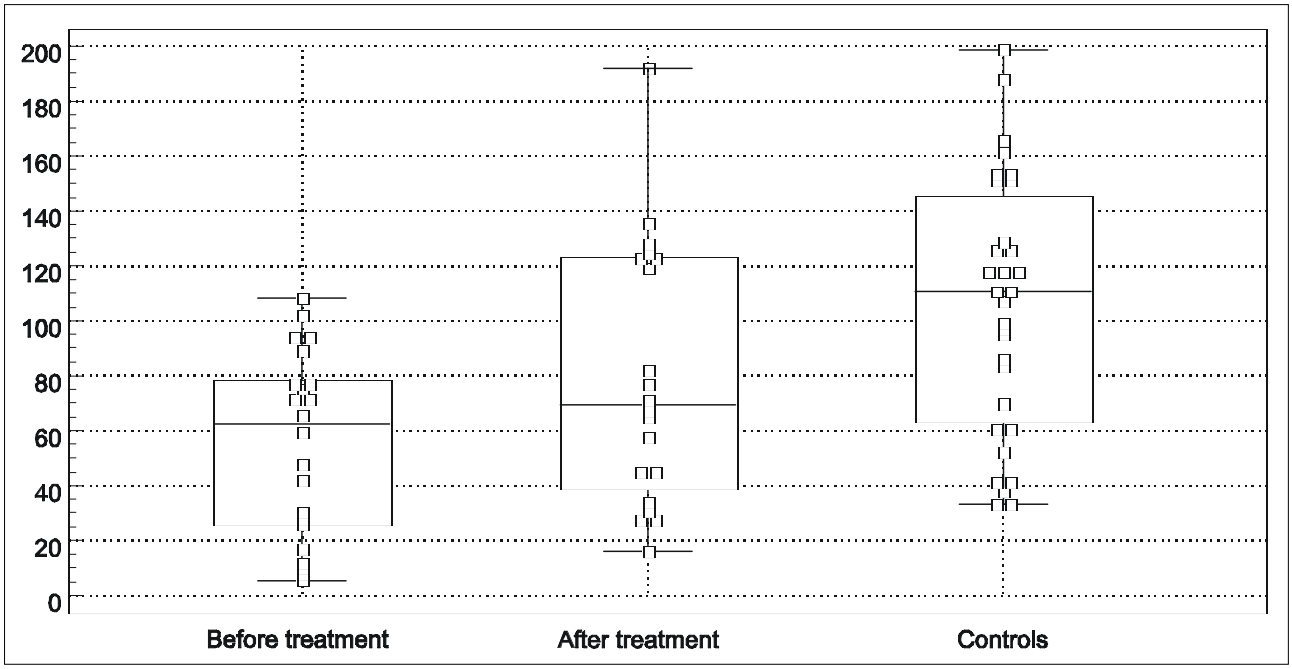
Table 1. Values of inhibin B, FSH, LH, testosterone, before and after antileukaemic treatment in prepubertal boys and in the control group.

	Before treatment	After treatment	Controls
Inhibin B (ng/l)	55.81 ± 33.74*	79.55 ± 47.39	105.89 ± 46.61
Testosterone (ng/dl)	13.58 ± 4.96	29.83 ± 36.5	25.9 ± 20.17
FSH (mIU/ml)	1.53 ± 1.19	2.31 ± 4.19	2.5 ± 1.8
LH (mIU/ml)	0.6 ± 0.7	1.43 ± 4.16	0.7 ± 0.9

*p<0.0002 between the values obtained before treatment and controls

Figure 1. Inhibin B values before and after treatment vs. controls



chemotherapy, the values of inhibin B augmented slightly (79.55 ng/ml ± 47.39), p<0.06 but remained lower than those in the controls (p<0.07). Tab 1. Fig.1.

We did not observe any differences in FSH, LH and testosterone values either before or after the treatment or in comparison to respective values in the controls. Tab.1.

We did not find any correlations between inhibin B and FSH values either before (r = -0.39 p = 0.21) or after the treatment (r = 0.31 p < 0.21).

Discussion

Examination of testicular function is easy in pubertal and post-pubertal boys, using routine hormone assays, whereas in prepubertal boys, it is difficult, due to a low activity of the hypothalamic-pituitary-gonadal axis. The measured level of serum inhibin B seems to be a good marker of testicular function, not only in adult men but also in young, prepubertal boys. During infancy, serum inhibin B is high and gradually decreases to the nadir at 6-10 years of age and, after an increase in early adolescence, it reaches a plateau in age 12 to 16 years. In younger age, inhibin values rest independent of FSH values, whereas an inverse relationship between inhibin B and FSH appears in puberty [2].

Cytostatics, especially alkylating agents, such as cyclophosphamide, cisplatin, procarbazine and/or abdominal irradiation, cause gonadal damage, inhibit DNA synthesis in differentiating spermatogonia, induce germinal aplasia and cause the absence of sperm in seminal fluid [1, 3]. Sperm production is more susceptible to damage at very low doses of irradiation (>1.2 Gy), whereas Leydig cell function is usually preserved up to 12 Gy [1]. Taking into consideration that Sertoli cells are more affected during anticancer treatment, it seems that inhibin B is a good marker to monitor the chemotherapy-induced testicular damage in adults, as well as in children [3].

The influence of age or pubertal stage at the time of treatment on a gonadal function in future has been discussed [4, 5]. Prepuberty, in predominant opinions, does not protect the male gonads from the late effects of chemotherapy, although some analysis suggest that prepubertal boys would be more resistant than adults to the effects of chemotherapy [1, 4]. Crofton et al. found normal values of inhibin B in prepubertal boys (before, during and after the treatment) [4]. In Kenney et al.'s opinion, infertility could be observed irrespectively of the pubertal status at the time of treatment in men, treated with high (>25g/m2) doses of cyclophosphamide [6].In our analysis, concerning prepubertal boys, we observed lower values of inhibin B at the time of diagnosis, comparing to respective values in the controls. The results, obtained some years after the end of the treatment, indicated a tendency towards higher values of inhibin B, in comparison to the results before the treatment (in the second part of analysis, more patients were in the 2nd stage of puberty). It suggests a possibility that a part of stem spermatogonia can survive

the cytotoxic treatment and spermatogenesis can restart after some years. Byrne et al. observed normal fertility in men, treated during childhood for ALL except for the men, receiving cranial irradiation (24Gy) before the age of 10 years [7]. In our group, cranial irradiation was not used.

We did not find any changes in either LH or testosterone production, which affirms the observation that Leydig cells are less susceptible to chemotherapy than Sertoli cells [1].

It is difficult to explain the low values of inhibin B in children at diagnosis. Semen abnormalities were found by Rueffer et al. in men with advanced stage of Hodgkin's disease prior to treatment. The authors suggested gonadal damage either by the disease itself or by cytokines, influencing spermatogenesis [8]. None of the patients in our group had, at diagnosis, any clinical symptoms of testicular infiltration by leukaemic process. This problem needs future observations in greater group.

In conclusion, haematological malignancy and its treatment influence gonadal function before puberty but with a possibility of recovery. During this period, inhibin B could be used as a sensitive indicator of testicular function.

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