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SUSTAINED GROWTH IN SPITE OF RADIATION INDUCED GHD OCCURS ONLY AFTER LOW HYPOTHALAMO-PITUITARY DOSE.

Normal growth, despite GHD, has been reported after cranial radiation (CR) for leukemia (ALL). In order to analyze the characteristicsof the patients with GH peak <5 ng/ml after AITT, 2 groups were investigated: group I with 24 Gy for ALL (n=27) and group II with 30-50 Gy for face and neck tumors (n=17). All were prepubertal and received thyroxine treatment when necessary. Patients of groups I and II were similar for age at CR (5.3 ± 0.6 and 5.5± 0.8 yrs respectively) for interval time since CR (4.5±0.6 and 4.4±0.7 yrs) and for their mean GH response to AITT: 3.7±0.2 and 3.7±0.3 ng/ml. Growth retardation of 1SD or more was found in all patients of group II and in 17/27 cases of group I. Normal growth was observed only in 10 cases of group I in spite of GH peak to AITT < 5 ng/ml. GHD was confirmed during sleep in 2 of them : GH peak at 3.5 and 7.9 ng/ml. Weight for height was in the normal range.
In conclusion, these data show that normal prepubertal growth may occur in spite of GHD only after low radiation doses. They suggest that a residual low GH secretion may paradoxically be sufficient to promote growth in some patients by an unclear mechanism.

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GH-INSUFFICIENCY DEVELOPES WITHIN TWO YEARS AFTER CRANIAL IRRADIATION FOR A BRAIN TUMOR:

In a previous study we found that after two years or more post radiotherapy for a brain tumor (BT) all children investigated had a very low spontaneous GH-secretion. The aim was now to evaluate how soon after radiotherapy this GH-impairment occurrs.
For the last three years all prepubertal children (n=5) irradiated for a BT at our hospital have been studied every 6 months after irradiation with a 24h-GH profile immediately followed by a GHRH (1-29) test. Integrated 30 min samples over 24h were measured and analysed with Pulsar program.
Results: During 0,5 - 2 years post irradiation GH secretion in three children irradiated with 35-40 Gy to the hypothalamus, declined progressively whereas two children who had received 56 Gy showed a blunted secretion already at the first measurement.
After two years all children had a very low spontaneous GH-secretion; AUCb<100 mU/l and GH max < 14 mU/l. GH-response after GHRH declined gradually in each child during the two years but remained >30 mU/l. The growth rate decreased in all children.
Conclusion: This first longitudinal study performed during the first two years after irradiation for a BT supports the previous hypothesis that if GH-secretion is to be evaluated the appropriate time is at two years post irradiation. Before this time GH-secretion is heterogenous, probably due to the dose of irradiation delivered.

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ENDOCRINE DISORDERS DUE TO CRANIAL IRRADIATION

Effects of central nervous system (CNS) radiation on hypothalamic-pituitary function were studied in children with leukemia and brain tumors. Acute lymphatic leukemia (ALL): Twenty-one children in complete clinical remission were examined not earlier than 2 years following therapy, chronological age (CA) 10-14 yrs., CNS radiation dose 2100 rad. Results: Height SDS pretreatment +1.51, this value was significantly reduced posttreatment. - Basal and LH-RH-stimulated FSH levels were decreased in prepubertal patients and in pubertal girls. No significant differences with controls in T3, T4, TBG, basal and TRH-stimulated TSH and basal and TRH-stimulated prolactin values. Significant decrement in basal, circadian, lysinevasopressin (LVP)- and insulin-hypoglycemia (IH)-stimulated ACTH and cortisol levels. Reduced GH levels following (IH). Final adult height in 24 additional adolescents and adults in complete remission after ALL (CA 16-21.5 yrs., CNS radiation dose 2190 rad): Mean height SDS +1.05 ± 0.95.
Brain tumors (remote from pituitary area): Fifteen patients, CA 10.7-20.3 yrs., CNS radiation dose 1950-6000 rad. Results:Height SDS pretreatment +0.23, this value was significantly reduced posttreatment. Basal and LH-RH-stimulated LH and FSH values were reduced in pubertal girls. Normal T3, T4, TBG, basal and stimulated TSH and prolactin values. GH levels following arginine and IH were decreased. Diminished basal, circadian and stimulated (IH and LVP) ACTH and cortisol levels. - These findings suggest hypothalamic-pituitary dysfunction following CNS radiation.

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NEUROENDOCRINE ALTERATIONS INDUCED BY CRANIAL IRRADIATION (CR) IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA (LLA).

In order to investigate the effects produced by external CR on neuroendocrine systems,GH secretion,in response to hypothalamic stimulation (clonidine,0.15 mg/m2, per os) and to direct pituitary challenge (GRF-29,Serono,Spain,1 µg/kg,iv bolus), and TSH and PRL responses to TRH (200 ug,iv bolus) were evaluated in 7 children, 3 years after previous CR for LLA (dose= 2400 rads). Growth velocity was also periodically evaluated. Mean age at diagnosis was 4.2 years (range : 9 months to 8 y.). Hormones in plasma were measured by sensitive IRMA. RESULTS (mean ± SD).- Growth velocity,as expressed by SD under the mean for age, was impaired in all patients : -3.05 ± 1.8. GH peaks elicited by clonidine and GRF-29 were similar : 13.8 ± 6.1, and 15.5 ± 10.8,ng/ml,respectively.Either basal or stimulated TSH and PRL were between normal limits, TSH : 0' = 1.6 ± 1.1, peak = 7.8 ± 5.3,µU/ml; PRL : 0' = 5.4 ± 2.1, peak = 22.5 ± 14.8, ng/ml. Individually,while in 6 patients a normal GH response to clonidine was observed, 3 of them exhibited a poor response of the hormone to GRF challenge (peaks : 7.4, 9.2, 2, ng/ml). CONCLUSIONS.- The fact that GH secretion appeared to be normal when explored either from the hypothalamus or directly at pituitary level, suggests that CR (at the dose utilised) did not affect the endogenous GHRH-GH pathway. Given that,in spite of the fact that thyroideal status was also normal, growth velocity is consistently impaired in these children it is tempting to speculate that CR affected the suprahypothalamic structures that, governing the interplay between GHRH and somatostatin, lead to the normal pattern of spontaneous GH secretion. Additionally, the fact that in 3 cases there was not observed significant GH response to GRF,but normal response to clonidine, supports our previous hypothesis on HSR and GRF tests (Bevesa,J Endoc Inv,10,Suppl 3,27,87)

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ENDOCRINE CHANGES IN CHILDREN AFTER ALLOGENEIC BONE MARROW TRANSPLANTATION.

34 children 1-17 years at the time of bone marrow transplantation (BMT) have been followed regarding their endocrinological development at yearly intervals for at least 3 years. Diagnosis leading to BMT was leukemia (n=28) or severe aplastic anemia (SAA n=6). Before BMT all the patients were conditioned with cyclophosphamide and the leukemic children also had total body irradiation (TBI) 10 GY. Challenge tests with TRH, ACTH and LH-RH were given and cortisol response to insuline hypoglycemia was also evaluated. The children with SAA all exhibited normal function of their thyroid, adrenal and gonadal glands. The leucemic children showed some sign of thyroid dysfunction in 14/28 cases. All leucemic girls (n=12) show evident signs of gonadal damage. None of them have entered into spontaneous puberty and have extremely low values of oestradiol at ages when puberty should have started. Gonadotropin levels were extremely high. The boys show more variation in their gonadal effects. Boys, prepubertal at BMT, have entered spontaneous puberty in due time in 4/5 cases although with decreased testicular volume. The boys who had entered puberty at the time of BMT have retained normal testosteron values but their testicles have decreased in size. The adrenal cortex seemed to be intact after BMT, evident by normal responses of cortisol, DHA and 17-OH-progesteron after ACTH. In conclusion, TBI seems to cause endocrine changes in cildren undergoing BMT for leucemia. The gonads especially in girls and the thyroid gland are affected while the adrenal cortex seems to staynormal

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EVALUATION OF GROWTH AND ENDOCRINE FUNCTIONS AFTER BONE MARROW TRANSPLANTATION (BMI) FOR MALIGNANCIES.

Total body irradiation (TBI) is used in preparation for BMI and in order to evaluate the course of growth and endocrine disturbances an extensive follow-up has been designed. 17 children, aged 2.4-17.8 years received BMI for ALL (n=14), AML (n=2) and CML (n=1). Median height SDS in 14 children below age 15 was at time of BMI +0.48 (range -1.42 to 1.60) and after 12 months +0.12 (-1.16 to 1.20) ($p<0.05$). Those followed for 24 (n=9) and 36 months (n=6) had no significant fall in height SDS. Serum somatomedin C in the 6 cases followed for 36 months was normal. Peak growth hormone values after clonidine showed great variation and the results were inconclusive. Primary hypothyroidism was found in one case and elevated TSH values in 3 with T4 in normal range. No evidence of TSH insufficiency was seen. In all 8 girls above 10 years ovarian insufficiency developed and all were in need of replacement therapy. Of 2 boys above 10 years one had subnormal serum testosterone and one had bilateral orchiectomy performed. 6 of 7 boys below 10 years had normal gonadotropin response to LHRH and one was hyperresponsive. No evidence of gonadotropin insufficiency was found. Although preliminary, our data show that growth retardation does not seem to be of major importance whereas gonadal deficiency is pronounced and thyroid deficiency may be frequent. More data are needed and a detailed and prolonged endocrine follow-up seems essential.