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EFFECTS OF L-T4 THERAPY WITHDRAWAL ON GONADOTROPIN SERUM LEVELS IN L-T4 SUBSTITUTED HYPOTHYROID PATIENTS

Elevated serum LH levels and increased LH:FSH ratio which return to normal under L-T4 therapy are frequently observed in longstanding primary hypothyroidism and may account for the findings of precocious puberty and cystic ovaries in hypothyroids (Lindsay et al, Am J Dis Child 134, 588, 1980). In 10 congenital hypothyroid subjects aged 7 to 18 yrs (6 prepubertal girls and 4 pubertal boys), L-T4 treatment was discontinued for a 3-week period in order to perform thyroid scan. All of them underwent iv LH-RH-test immediately before and 20 days after the therapy withdrawal. All the blood samples were processed in the same run. The shifting of TSH, T4 and T3 serum values from the euthyroid to the hypothyroid range was accompanied in all the patients by a significant increase in both baseline LH (12.9±4.7 vs 6.3±2.5 mIU/ml, 2 $p < 0.001$) and PRL (22.6±11.7 vs 11.6±3.0 ng/ml, 2 $p < 0.05$) plasma levels On the contrary LH peak after LHRH (22.5±7.9 vs 20.1±10.4) and either basal (2.4±1.5 vs 3.2± 2.1 mIU/ml) or stimulated (7.9±2.0 vs 6.8±2.0) FSH concentrations were not affected by L-T4 withdrawal. These results indicate that: a) an evident increase in LH serum levels precociously occurs in response to thyroid failure; b) such increase does not reflect an enhanced sensitivity to LHRH; c) it may reflect anomalous LH reactivity to TRH (De Luca et al, Ped Res 18, 1222, 1984) or abnormal clearance (Lindsay et al).

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HYPOPHYSEAL-THYROID AXIS FUNCTION IN EPILEPTIC CHILDREN ON ANTICONVULSANT MONOTHERAPIES.

Antiepileptic drugs have been inconstantly reported to involve thyroid hormone synthesis and/or metabolism.

We have performed a TRH test in 25 children of both sexes, aged 5-13 1/2 years, clinically euthyroid, on unchanged monotherapy from the start (at least 2 years).Serum basal levels of TSH, T_4, T_3, TBG and serum TSH levels after TRH were assayed by commercial RIA kits.Statistical analyses included mean,SD, Student's t test.

Valproate-treated children (VPA-C) (10 subjects) showed TSH levels both before ($p<0.05$) and after TRH ($p < 0.01$ or 0.001) higher than normal children (NC). Serum T_4 levels in VPA-C, carbamazepine-treated children (CBZ-C) (7 subjects) ($p<0.001$) and phenobarbital-treated children (PB-C) (8 subjects) were lower than in NC ($p < 0.01$). PB-C had higher T_4 levels than CBZ-C ($p < 0.01$).

Our data show a subclinical primary hypothyroidism in VPA-C. Low T_4 with normal TBG and normal levels of TSH both before and after TRH in CBZ-C and PB-C could be explained by a decreased thyroidal synthesis and/or an enhanced peripheral metabolism with a concomitant depressive influence on hypothalamic-pituitary axis or a T_3-depending cellular euthyroidism.

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DIMINISHED TSH SECRETION ASSOCIATED WITH NEONATAL THYROTOXICOSIS

We report 3 1/2 year old twin boys with prolonged neonatal thyrotoxicosis and persistently low TSH secretion manifested by a diminished TSH response to hypothyroxinemia and to TRH stimulation. Features of neonatal thyrotoxicosis included: intrauterine growth retardation, microcephaly with ventriculomegaly, poor weight gain, hyperphagia, irritability, diarrhea, exophthalmos, tachycardia, hepatosplenomegaly, and direct hyperbilirubinemia. However, there was no goiter or history of maternal thyroid disease and diagnosis was delayed until 11 weeks of age (T_4>29 ug/dl, T_3>580 ng/dl). By age 6 mo., on propylthiouricil (PTU) 25 mg b.i.d., both infants had TSH levels <2 uU/ml (normal N=0.4-4.5) despite T_4 levels <1 and 3.1 ug/dl (N=7.2-15.6) and free T_4 (FT_4) levels of 0.3 and 0.5 ng/dl (N=0.8-1.9). At 3 4/12 years, while on PTU 50 mg q.i.d., they again became hypothyroid with FT_4s of <0.2 and T_3RIA of 47 and 43 ng/dl (N=80-220) with a TSH of 3.5. A TRH stimulation test revealed baseline TSH values of 8.5 and 11 and maximal stimulation values of 11 and 14. Normal hGH responses to L-Dopa (8.7 and 13.1 ng/ml), fasting A.M. cortisols (12.6 and 14.1 ug/dl), and normal genitalia make other pituitary hormone deficiencies unlikely. The diminished TSH responses to hypothyroxinemia and TRH stimulation indicate that the capacity to synthesize TSH, or the set point for pituitary-thyroid feedback control, may be altered by excess thyroid hormone concentrations during a critical stage of development.

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HETEROGENEITY IN JUVENILE THYROTOXICOSIS

In this study we have examined factors, present at diagnosis of juvenile thyrotoxicosis, for their possible prognostic significance with respect to outcome of anti-thyroid drug therapy. Thirty-six children (<17 years) were diagnosed and treated during 1972-1982. The material was characterized with respect to sex, age, tissue type (HLA-B8/DR3), thyroid hormone values, autoantibodies (TSH-receptor antibodies, TRAK; microsomal and thyroglobulin antibodies) and thyroid fine-needle biopsy at diagnosis. Mean period of anti-thyroid therapy 33 months, mean follow-up period 67 months. 22 pat. (61%) have either relapsed following withdrawal of antithyroid treatment (17/36) or have had to undergo surgery because of large goiter and/or poor response to medication (5/36). The remaining 14 pat. (39%) are still in remission. In the relapse vs remission group the presence of TRAK was 74% vs 18% and a lymphocytic thyroiditis at biopsy 33% vs 64%. None of the other factors examined at diagnosis differed. At follow-up the material was re-evaluated with biopsy and autoantibodies. Evidence of Hashimoto's thyroiditis (H) was found in six patients all in remission. The other pat. were classified as Grave's disease (G) and only 8 (27%) were in remission. It is obvious that there is a need for better diagnostic and prognostic tools to avoid long term treatment in H. and consider alternative therapy in G.

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FOLLOW UP OF JUVENILE HYPERTHYROIDISM: THYROID FUNCTION AT SHORT-TERM AS PREDICTOR OF THE EVOLUTION.

At present, no laboratory test is available to predict the evolution of Graves' disease. A follow up of 1 to 14 y.in 59 patients aged 2 4/12 to 17 y..old ($\bar{X}$±SD: 9.4±3.9) is presented. They all received antithyroid drugs as initial treatment, 7 were treated with ^{131}I for intolerance or social problems. Thirty six patients followed for 3 to 14 y., could be reevaluated with T4, T_3 and TSH and/or TRH after treatment in at least 2 occasions, at short term (ST: 1-2 y. post onset of treatment) and at long term (LT: more than 3 y.; $\bar{X}$: 6.2±3.3). According to thyroid status at ST and LT respectively 3 groups were found: I) hyperthyroidism (Hper) and Hper n=23, 64%; II) Hper and hypo or euthyroidism (Hpo/Eu) n=4, 11%; III)Hpo/Eu and Hpo/Eu n=9, 25%. No patient changed from Hpo to Hper. Eighty nine percent of patients did not modify their thyroid function between ST and LT. The influence of age at admission on persistence of Hper 3 y. later was also studied. Fourteen out of 16 patients (87.5%) less than 8 y. were still Hper while only 14 out of 24 (58.3%) were Hper after 8 y. old. It is concluded that evaluation of thyroid function at ST is useful to predict thyroid status at LT since 90% of patients showed no variations. Patients developing Graves' disease before the age of 8 y. have a high chance of remaining Hper 3 y. later. If Hper persits at ST evaluation, the possibility of ^{131}I adminstration should be considered to avoid the excessively long treatment required by the unrelenting course of this disease.

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THYROID VOLUME IN CHILDREN

Goiter grading according to WHO standards is a rather crude method used for population studies mainly. In the individual child where usually smaller goiters of grade Ia and Ib are diagnosed it might be difficult to define absence or presence of goiter by palpation and inspection alone. The purpose of this investigation was to obtain normal thyroid volumes by means of ultrasonography in healthy children of various ages and to compare these volumes with a group of goitrous children. A total of 621 children (322 girls, 294 boys) of 6 to 16 years of age was investigated. 278 (157 girls, 121 boys) had a goiter on physical examination. Ultrasonography was performed at school using a portable realtime scanner with 4 MHZ linear transducer. Volume was estimated on the basis of ellipsoid thyroid configuration. In healthy boys total thyroid volume increased from 1.8 ± 0.6 (M±SD) to 8.4 ± 3.4 ml from 6 to 16 years respectively, in girls the volume changed from 2.3 ± 1.3 to 10.5 ± 5.1 ml from 6 to 15 years respectively. Goitrous children had larger volumes. There was however a strong tendency for overdiagnosis on clinical basis. A short obese neck prevents the goiter from clinical detection whereas a rather long and lean neck may lead to clinical overdiagnosis. In summary normal thyroid volumes of children were provided by means of sonography which represents the best suitable method to assess volume changes following treatment procedures.