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THYROID FUNCTION DURING L-T4 THERAPY IN CHILDREN WITH CONGENITAL HYPOTHYROIDISM (C.H.).

Thyroid function was evaluated in 28 (15 prepubertal and 13 pubertal) clinically euthyroid children with C.H. on L-T4 treatment. Patients were divided in two groups (A=suppressed and B=not suppressed) according to their TSH response to TRH i.v. 20 prepubertal and 30 pubertal normal children served as control group (C). T4,T3,FT4, and rT3 have been measured by RIA, TSH by IRMA. All results are expressed as x±SD. In the prepubertal group, 8 had suppressed TSH to TRH (Δ TSH <4 uU/ml) and 7 normal (Δ TSH=4-16 uU/ml); in the pubertal group 7 were suppressed and 6 normal. L-T4 therapeutic regimen was identical in both A and B group (2.9±0.8 vs.2.9±0.7 µg/kg/day). TSH serum levels were lower ($p<0.01$) in group A (0.3±0.3 µU/ml) compared to both group B (2.7±1.5) and C (2.9±1.4). In all C.H. patients basal TSH was correlated ($r=0.8$ $p<0.01$) with TSH. In comparison to C, FT4 was higher ($p<0.01$) in group A (13.8±2.2 vs.9.7±1.9 pg/ml) whereas T3/T4 index was lower ($p\leq0.01$) both in group A and B (0.14±0.02 and 0.14±0.03 vs 0.2±0.04).In group A all prepubertal patients showed lower T3 and higher rT3 levels ($p<0.01$) compared to the matched controls (1.4±0.2 vs.1.7±0.2 and 0.4±0.1 vs.0.2±0.1 ng/ml). In conclusion, both TSH and FT4 seem to be good parameters in monitoring overtreatment in C.H., although TSH appears more useful in the single case. Moreover particularly in prepuberty the peripheral monodeiodination is the first compensatory mechanism, present even in the absence of TSH suppression.

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THYROTROPIN (TSH) SUPPRESSIBILITY IN CONGENITAL HYPOTHYROIDISM (CH).

Despite adequate replacement of thyroid hormone (TH), patients with CH often exhibit high TSH levels. We identified 16 clinically euthyroid patients with CH, 1.4-10 years of age, whose total thyroxine (TT_4) was 9.4-15.1 µg/dl (normal 5.0-12.2) or free T_4 (FT_4) was 1.6-2.2 ng/dl (normal 0.7-1.9), yet whose TSH was 8-60 µIU/ml (normal <4). Fourteen of 16 had thyroid aplasia, compared to 35% aplasia in CH. Five patients underwent a short TSH suppression test: TH dose was doubled for 7 days, followed by drug withdrawal and daily determinations of TSH and TT_4 or FT_4 for 10 days. Five patients underwent a long suppression test: TH dose was doubled for 7 days, followed by a return to the previous dose and weekly determinations of hormones for 5 weeks. TSH threshold was defined as the FT_4 level when TSH increased >4 µIU/ml. TSH threshold was 1.63±0.44 ng/dl FT_4 after suppression, compared to >1.99±0.18 ng/dl FT_4 before suppression ($p<0.005$) and to normal FT_4 levels of 1.3±0.6 ng/dl ($p<0.001$). By standardization of TSH threshold onto the calculated TH dose, the optimal dose of L-thyroxine was calculated to be 5.6±1.7 µg/kg. Conclusions: 1) Severe hypothyroidism in the fetus and infant results in high TSH thresholds. 2) Suppression with high-dose TH decreases TSH threshold. 3) TSH suppression allows calculation of optimal TH replacement. 4) TSH suppression is recommended to regain TSH levels as a means to monitor treatment.

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EFFECTS OF LONG-TERM TRH ADMINISTRATION IN PATIENTS WITH IDIOPATHIC HYPOTHALAMIC HYPOTHYROIDISM (IHH).

Since TRH deficiency accounts for clinical and biochemical picture of IHH, the etiological therapeutic approach to this rare disease should be TRH administration. After informed consent from parents, we administered TRH p.o. to 3 patients with IHH at the dose of 20 ng/day for 25 days and then 10 mg. every other day for 3 months, in order to avoid the well-known phenomenon of pituitary desensitization. During the first period all patients showed a marked increase in TSH secretion, when monitored 3 hrs. after TRH administration (basal: 4.1, 5.9,and 27.2; peak: 16.4, 16.3 and 69.7 mcU/ml, respectively). Consequently, FT3 and FT4 levels increased, reaching the normal range at different intervals; only in one patient FT3 and FT4 values were in the normal range over all the treatment period. After TRH withdrawal basal hormone levels fell to pretreatment values with the exception of TSH which was consistently lower (0.9, 1.1 and 6.3 mcU/ml, respectively), thus demonstrating a pituitary desensitization. During the second period all patients had an increase in TSH levels but only in one case a sustained normalization of FT4 levels was seen. No side effects were noted. In conclusion, the present data 1) confirm that TRH as daily therapy restores a transient euthyroid state in patients with IHH; 2) demonstrate that, at the dose and time schedule we used, long-term TRH administration does not seem effective in the treatment of IHH, because of pituitary desensitization; and 3) suggest that L-Thyroxine replacement therapy still remains the most reliable treatment of this disease.

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JUVENILE AUTOIMMUNE THYROIDITIS (JAIT) IS ASSOCIATED WITH HLA-DR4.

The associations of Hashimoto's goitrous thyroiditis with HLA-DR5, atrophic thyroiditis with DR3, postpartum thyroiditis with DR4 and Grave's disease with DR3 have been described. We studied HLA-A,B,C,DR antigens, C4 and Bf types and thyroid function in 64 patients with JAIT. 45 of them were young adults with a mean follow-up of 10.6 years (J Pediatr 1985;107:898), others were 9.6-17.5 years of age and were followed for 2.3 (0.5-8.5) years. The HLA-DR antigen frequencies in patients (and controls) were: DR1 20% (37%) $P < 0.01$, DR2 24% (33%), DR3 32% (32%), DR4 54% (27%) $P < 0.001$, DR5 3% (6%), DR6 10% (5%), DR7 14% (17%) and DR8 3% (13%) $P < 0.05$. Euthyroidism was found in 53%, subclinical hypothyroidism in 14% and clinical hypothyroidism in 33% of the patients. Circulating antimicrosomal antibodies (Msab) (titre ≥ 400) were present in 73% and antithyroglobulin antibodies (titre ≥ 400) in 38%. Of the 17 patients with absent or low titre Msab 16 were euthyroid ($P < 0.001$) and 13 of them were DR4 positive ($P < 0.05$).
Conclusion: JAIT is highly significantly associated with HLA-DR4 and euthyroidism with absent or low Msab titre.

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FAMILIAL HYPERTHYROIDISM DUE TO INAPPROPRIATE TSH SECRETION: A SEX LINKED DOMINANT TRAIT

Studies in 2 non-related Sephardic Jewish families, one of which extended over 5 generations, revealed 9 females with clinical and/or biochemical hyperthyroidism due to inappropriate TSH secretion. Age at diagnosis ranged from early infancy up to 80 years, the youngest case being detected by measuring elevated thyroid hormones and TSH on a filter paper specimen obtained for routine screening for neonatal hypothyroidism. Except in one case, the clinical manifestations became apparent at adolescence and were more severe in older patients than in younger ones. Yet, these were in general milder than those found in classical Grave's disease. In 4 instances the disorder was diagnosed when symptoms recurred after subtotal thyroidectomy. None had a pituitary tumor. All subjects had elevated levels of thyroid hormones and prolactin (T4: 14-22 ug/dl, T3: 220-320 ng/dl, T3 Uptake: 41-65 %, TSH: 5-26 uU/ml, prolactin: 15-75 ng/ml). TRH further stimulated TSH and prolactin, resembling the response in hypothyroidism. T3 (25 ug/tid) given for one week reduced T4, T3 and TSH (measured 16 h after the last dose), but T4 (given in equimolar amounts in 2 patients) did not supress any of these parameters. Long term therapy with a single AM dose of T3 (25-50 ug) was given to 6 symptomatic patients. All became clinically and biochemically euthyroid after 3-4 months of therapy, and remained normal since then (up to 7 years). Inappropriate TSH secretion seems to be due to partial unresponsiveness of the thyrotroph to thyroid hormones. The defect may reside in a deficient pituitary T4 monodeiodinase (resulting in low intracellular T3 levels) or in a thyrotroph which has reduced sensitivity to T3. Genetic analysis reveals that X-linked dominance is the most likely mode of inheritance. Calculation of the variance of the expectancy (by the Fisher Exact Test) was highly significant ($p- <0.015$), indicating that the exclusive prevalence of the mutant gene in females does not occur at random.

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CONGENITAL HYPERTHYROIDISM DUE TO INAPPROPRIATE SECRETION OF THYROID STIMULATING HORMONE

The Syndrome of inappropriate secretion of TSH is a rare disease and has been described as a heterogenous group of disorders in juvenile and adult patients who show elevated TSH levels in the presence of elevated thyroid hormone levels.
We have observed an infant at age six weeks with congenital goiter who suffered from typical symptoms of hyperthyroidism. In spite of elevated T3 and T4 levels TSH showed basal values between 2 and 8 mU/ml.After TRH-stimulation TSH ranged between 39 and 100 mU/ml. Pituitary adenoma was ruled out; there appeared no relation to Graves' disease.
A long term therapeutic trial was performed with the analogue D-thyroxine. TSH gradually returned to normal and the goiter disappeared. After 6 years of observation the physical and psycho-intellectual development and the bone age have been stated to be normal for chronological age, although laboratory data indicated elevated thyroid hormone levels for years.
CONCLUSION: Up to now there is evidently no other report on congenital hyperthyroidism due to inappropriate TSH-secretion. Partial pituitary and peripheral thyroid hormone resistance appears to be likely. The long term therapeutic trial with D-T4 has proven to be successful.