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NORMAL SERUM T3 POSTNATAL SURGE AND INCREASED REVERSE T3 LEVELS IN SELENIUM-DEFICIENT RAT PUPS. JP Chanoine, S Alex, S Stone, SL Fang, JL Leonard and LE Braverman. Depts of Endocrinology and Physiology, Univ Mass Med Center, Worcester, MA 01655, USA and Dept of Paediatrics, Free Univ Brussels, B1020 Brussels, Belgium.

In adult rats, selenium (Se) deficiency markedly decreases liver type I outer-ring 5' deiodinase (5'D-I, a selenoenzyme converting T4 into T3), resulting in a 40% increase in serum T4 concentrations. Serum T3 and reverse T3 (rT3) concentrations are unchanged or marginally decreased or increased, respectively. In rat fetuses, serum T4 and rT3 concentrations are not affected by selenium deficiency. We studied the effect of Se deficiency on thyroid function in the rat neonate. 28 weanling female rats were fed a Se replete (Se+) or Se deficient (Se-) diet for 4 wk prior to mating and throughout gestation. 2-3 pups from each litter were sacrificed 7, 14 and 21 days after delivery. Serum T4, T3, rT3 and TSH concentrations and liver 5'D-I activity, to assess Se deficiency, were measured.

	7days		14days		21days	
	Se+	Se-	Se+	Se-	Se+	Se-
T4 (µg/dl)	2.2(0.1)	2.3(0.1)	6.8(0.3)	7.8(0.4)	8.7(0.5)	10.4(0.3)*
T3(ng/dl)	18(4)	15(3)	63(5)	56(4)	103(8)	113(23)
rT3(pg/ml)	242(31)	390(28)*	184(19)	323(25)*	104(16)	269(23)*
TSH(mU/L)	38(1)	40(2)	55(4)	47(3)	50(3)	50(2)

*P<0.001 compared to corresponding Se+ group Mean(SE).

In Se- pups, the decrease in 5'D-I activity was >89% confirming Se deficiency (P<0.001). In contrast to adult rats, Se deficiency causes no increase in serum T4 in 1 and 2 wk old pups and only a 20% increase in 3 wk old pups, but results in a 60-250% increase in serum rT3. Conclusion: 1) In the rat neonate, the 500 to 600% surge in serum T3 levels observed physiologically after birth is independent of liver 5'D-I activity, strongly suggesting that T4 to T3 conversion by peripheral tissues is not a major source of T3 in the neonate; 2) In contrast, serum rT3 levels increase markedly in Se- pups as early as the 7th postnatal day, suggesting that liver 5'D-I is important in rT3 metabolism.

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OUTCOME OF 3 SIBLINGS WITH ANTIBODY-MEDIATED TRANSIENT CONGENITAL HYPOTHYROIDISM. D. Pacaud, C. Huot, A. Gattereau, R.S. Brown, J. Glorieux, J.H. Dussault and G. Van Vliet, Univ. de Montréal et Univ. Laval, Quebec, Canada and Univ. of Massachussets, Worcester, Mass, USA

Transient neonatal hypothyroidism due to transplacental transfer of maternal TSH receptor blocking antibodies (TBIIs) is a rare cause of congenital hypothyroidism. A woman with hypothyroidism secondary to Hashimoto's thyroiditis diagnosed and treated since age 15 y delivered three babies at age 21, 23 and 25 y. TBII titers were very high throughout this period in the mother and in the newborns. All three babies (2 boys, 1 girl) had high TSH on newborn screening (Table in SI units) and were started on thyroxine replacement (8-12 µg/kg) at age 16 d (#1 and 2) and 3 d (#3).

#	TSH (screening)	T4	TSH	T4 (diagnosis)	FT4	Bone Age	99Tc Scan	US (cm^3)
1	205	65	278	57	N.D.	Retarded	N at 3 y	N.D.
2	154	88	106	N.D.	10	Normal	N at 16 d	0.95
3	23	123	51	N.D.	13.9	Normal	N at 3 d	1.53
N	<15	77-174	<10	86-193	9-27			0.4-1.3

Treatment was stopped at age 33 mo in sib #1 and at age 15 mo in sib #2; both have remained euthyroid since. In addition, #1 had atrial septal defect, #2 had unilateral renal agenesis, and #3 died at 10 w of a complex cardiac malformation. During pregnancy #1, maternal TSH levels were all normal, whereas during pregnancies #2 and #3, they were elevated (8-20 mIU/l). Developmental evaluation of sib #1 at age 4 y showed an IQ of 91 (Mc Carthy test), while sib #2 at age 2 1/2 y had a motor deficit (Bailey scale: motor 72, mental 88). **Conclusions**: transplacental transfer of TBIIs in this family was associated with 1) transient neonatal hypothyroidism in all children, with normal thyroid size at birth; 2) various congenital malformations in all children; 3) a developmental outcome that appeared related to maternal TSH levels but not to severity of hypothyroidism at diagnosis.

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NEUROLOGICAL, NEURORADIOLOGICAL AND NEUROPSYCHOLOGICAL EVALUATION OF PATIENTS WITH CONGENITAL HYPOTHYROIDISM (CH) AT 15-YEARS. J. Roy, J Puymirat, G. Van Vliet, J. Doyon and J.H. Dussault, Réseau Provincial de Médecine Génétique du Québec, (Laval University and University of Montreal).

To evaluate the long term consequences of congenital hypothyroidism, we have developed a detailed neurological, neuroradiological and neuropsychological study on 15-year old patients with CH detected by our screening program. The cohort consisted of 8 girls and 2 boys (mean age: 15). Mean age at initiation of treatment was 35 days. The control group consisted of older sisters or brothers (mean age 17). For the neurological assessment , we examined the motor functions, the sensorimotor apparatus, the reflexes, the cerebellar functions and the vestibular functions. The neuropsychological evaluation included the IQ, the memory, the verbal, the attentional and the frontal functions. Finally, patients with CH (but not their sibs) were explored by brain magnetic resonance imaging (MRI). The neurological and MRI evaluation was normal for 9 patients whereas one patient had minor cerebellar dysfunction in association with moderate cerebellar atrophy on MRI. The neuropsychological evaluation reveals no significant difference between the hypothyroid and control group for global IQ (mean for both group: 103), memory, verbal, frontal and attentional functions. However, 4 patients with CH had lower performances than their sibs, specifically for the attentional and frontal tests. Patients with lower IQ at 5 years also had lower IQ at 15 years. No correlation was found between the neuropsychological performance and the levels of T4 at diagnosis nor with age at initiation of treatment. This study confirms our previous results showing that some patients with CH have still minor neurological and neuropsychological manifestations despite early treatment.

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EFFECT OF THYROID HORMONE TREATMENT ON THYROMEGALY IN CHILDREN AND ADOLESCENTS WITH HASHIMOTO'S THYROIDITIS. K. L. Rother, D. Zimmerman, and W. F. Schwenk, Department of Pediatrics, Mayo Clinic and Foundation, Rochester, MN 55905, U.S.A.

The effectiveness of thyroxine treatment in childhood to reduce thyromegaly in Hashimoto's thyroiditis is controversial. Previous data are based on responses of both adults and children, and thyroid function is frequently not well documented. The present study was undertaken to determine whether certain subgroups of children with goitrous Hashimoto's disease might more readily show a reduction in the size of their thyroid glands when treated with thyroid hormone. Sixty-nine patients ≤ 18 years of age evaluated since 1982 with antibody proven Hashimoto's disease and more than minimally enlarged thyroid glands were identified. All patients were followed for ≥ 1 year and examined by palpation at least twice in the 12 month period after diagnosis. Only clearly identifiable changes in thyroid gland size were used to categorize patients. Thirteen of 50 patients treated with thyroxine were euthyroid prior to therapy; in no case did treatment affect gland size. A different response ($p < 0.001$) was observed in the 21 hypothyroid children: 16 (76%) had a reduction of their gland size while only in 5 (24%) patients thyromegaly persisted without change. Of 16 treated patients with compensated hypothyroidism (mean TSH 16.4 ± 3.9 mU/L), 12 (75%) showed no change and 4 (25%) a reduction. Variable courses independent of TSH levels were observed in the 19 untreated patients: smaller in 5 (26%), unchanged in 10 (53%) and larger in 4 (21%). We conclude that only hypothyroid children with Hashimoto's disease respond to thyroxine treatment with a reduction of thyromegaly (in 76% of cases), whereas no significant benefit of treatment could be shown in patients with normal plasma thyroxine levels prior to therapy regardless of TSH levels.

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GROWTH HORMONE (GH) RECEPTOR IMMUNOREACTIVITY IN CARTILAGE AND BONE OF GROWTH-RETARDED HYPOTHYROID (HT) RATS.

HT results in diminished GH synthesis, increased liver GH receptors, growth retardation with narrowing of the growth plate and osteopenia. We examined the immunoreactivity (IR) of GH receptors (R) in tibiae of normal young rats, and compared them with rats, rendered HT by methymazole for 7 wk, with or without GH or L-thyroxine (T_4) replacement over the last 2 wk, to demonstrate 'catch-up' growth. The avidin-biotin-peroxydase method was used to localize GH-R, tagged with monoclonal antibody to the GH-R (MAb 263). Quantitative analysis was made by antibody dilution. HT and replacement efficacy were varified by serum T_4 and T_3 levels. HT rats' growth was stunted, and GH therapy induced 'catch-up' growth, to half of that of T_4 replacement. Pituitary GH levels were nullified in HT. In normal rats GH-R IR was localized at the resting chondroprogenitor cells and in mature hypertrophic cells of the growth plate, but not in proliferating chondroblasts. It was also present in articular cartilage, in osteoblasts, osteoclasts, some osteocytes of the metaphyseal bone, and various components of the bone marrow. In HT bones GH-R were also evident in proliferating flat chondroblasts of the growth plate. GH-R IR was >4-folds higher in HT growth plate and bone compared with normal. GH replacement decreased the intensity of GH-R in both chondrocytes and osteoblasts, and T_4 replacement normalized it. It is concluded that bone and cartilage GH-R increase in HT, due partly to the accompanied GH-deficiency, and partly through direct T_4 effect in cartilage and bone.

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PAPILLARY THYROID CANCER IN CHILDREN. D. Zimmerman, I. Hay, and E. Bergstralh, Department of Pediatrics, Division of Endocrinology, and Section of Biostatistics, Mayo Clinic, Rochester, MN 55905, USA

Papillary thyroid cancer has been reported in large numbers of children from regions close to the Chernobil nuclear explosion. The papillary thyroid cancer in these children has been reported to be more aggressive than are similar tumors arising in other settings. To examine the effect of previous radiation therapy on aggressiveness of childhood papillary thyroid cancer, we examined the records of 90 children (66 girls and 24 boys) less than 17 years of age receiving primary surgical treatment for papillary thyroid cancer at the Mayo Clinic between 1940 and 1990. 21 patients (23%) had received previous radiation therapy—usually comprising low-dose external beam radiation for benign conditions such as thymic enlargement. Median followup was 30 years.

		Radiation	No Radiation	P Value
Grade of tumor	Grade 1	91%	95%	0.56
	Grade 2	9%	5%	
Size of tumor	< 4 cm	52%	81%	0.018
	> 4 cm	48%	19%	
Extrathyroidal invasion		28%	16%	0.19
Neck node metastases		100%	77%	0.015
Distant metastases		5%	4%	0.59

Conclusion: Children with previous radiation therapy had larger tumors and more frequent neck node metastases than did children without previous radiation. Grade of tumor, extrathyroidal invasion, tumor recurrence and mortality were not significantly different in radiated and nonradiated patients.