AUTOIMMUNE THYROIDITIS WITH SEVERE HYPOTHYROIDISM RESISTANT TO THE TREATMENT WITH HIGH PERORAL DOSES OF THYROXINE: CASE REPORT

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Female patient (42 yr) suffered from autoimmune thyroiditis resulting in severe hypothyroidism. She was treated for several years by district physician with the dose of 150 μg L-thyroxine daily. Since the level of TSH was repeatedly very high and no improvemenet of clinical signs has been observed, she was refered to the Medical Faculty Hospital. Thyroid ultrasound showed remarkable diffuse hypoechogenicity, thyroid scintigraphy showed enlarged thyroid with low ^{99m}Tc uptake, TRH test was normal, thin needle biopsy supported autoimmune thyroiditis. X-ray examination showed normal sella turcica and no changes in the pituitary were observed with computer tomography. In spite of increasing the dose of peroral L-thyroxine to 300 μg/d and later to 500 μg/d the clinical status and TSH level did not improve. The patient was originally suspected from malabsorption of thyroxine. However, the test with a large single peroral dose (1000 μg) of L-thyroxine showed a rapid decrease of TSH level (from 126 to 75 mU/l) and increase of total T_4 level (from 18 to 64 nmol/l) within 4 hr. Later the patient has been treated with intravenous L-thyroxine (500 μg every 3-4 days for 4 weeks) which resulted in the decrease of TSH level to 10 mU/l and increase of T_4 level to 80-100 nmol/l.

After that it was concluded that the problem is a poor compliance of the patient who apparently does not actualy take the medication, although she always claimed that she is doing so. Refering to some similar cases described in the literature the case was classified as thyroxine pseudomalabsorption. In spite that this problem has been explained to her and her relatives, she refused to take any medication and is consistently neglecting all invitations to further examinations.

Key words: Autoimmune thyroiditis – Hypothyroidism – Thyroxine pseudomalabsorption

Obviously, the hypothyroidism which appears to be resistant even to the treatment with high doses of L-thyroxine deserves some special attention. Theoretically, it may result from malabsorption of L-thyroxine from gastrointestinal tract or from poor compliance of the patient.

A variety of hypothyroidism with hardly detectable serum thyroid hormones and very high level of TSH has been repeatedly described. A majority of such cases is apparently due to TSH unresponsiveness as formulated first by Stanbury (1968). Molecular genetic analysis elucitaed the pathogenetic background of such cases by demonstrating inactivating mutations of the TSH receptor. Among them were two heterozygous siblings with missense mutations of the extracellular domain of TSH receptor producing partial TSH unresponsiveness with hyperthyrotropinemia (Sunthomithepvarakui et al. 1995). However, these siblings as well as other patients described later (de Roux et al. 1996; Clifton-Bligh et al. 1997) were euthyroid with either normal or low normal thyroid hormone levels. At the same time,

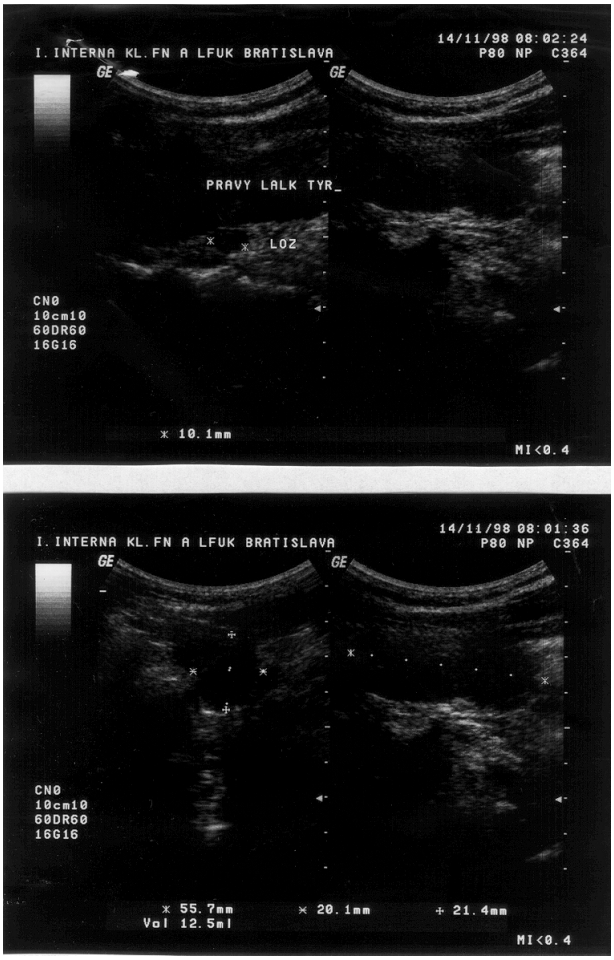

Fig. 1 Thyroid ultrasound image. Upper panel – right lobe (LOZ – nodule), lower panel – left lobe.

however, several cases of neonates or babies were described with inactivating TSH receptor mutations, permanently low serum thyroxine concentrations, markedly hypoplastic thyroid and overt hypothyroidism (Abramowicz et al. 1997; Bieberman et al. 1997; Gagne et al. 1998).

Recently Tomacchera et al. (2000) described a 22-yr-old female who was severely hypothyroid and mentaly retarded. Serum T_4 and T_3 were below the sensitivity of the methods and serum TSH was highly elevated. The thyroid was located in the normal position and did not respond to bovine TSH either by radioidoine uptake or release of thyroid hormones and thyroglobulin. Genetic analysis showed a homozygous inactivating mutation of the TSH receptor in the first extracellular loop. After 12 months of L-thyroxine (2.6 μg/kg/day) treatment TSH was undetectable both basally and after TRH administration and serum total and free T_4 and T_3 were at the upper limit of normal range.

Case Report

Family and personal history. Female patient 42 yr old. Her mother has been treated with success since about 20 years ago by thyroxine substitution because of hypothyroidism due to autoimmune thyroiditis. Her father does not have any thyroid disorder.

The patient suffers from obesity, had elective cholecystectomy in 1982 and was repeatedly treated for neurological problems related to vertebrogenic lumbalgia, cervicocranial syndrome and migraine. Recently she has night convulsions of the extremities. She had periodical constipation. Menstrual cycle is regular and normal. She never was pregnant. She does not drink alcohol, smokes 5-20 cigaretes daily, drinks 1-2 cups of cofee daily. She does not declare any signs of allergy.

Thyroid illness. Since 1992 she was treated for Hashimoto thyroiditis with L-thyroxine by local district physician on the recommendation and under the supervision of endocrinologist from the District Hospital. Since the initial daily dose of 100 μg L-thyroxine did not suppress the very high level of TSH, the dose of L-thyroxine has been increasing step by step to 150, 200 and 300 μg daily. At the same period (1992-96) she gained about 20 kg body weight within 1993-96 and felt some pressure and tension around the larynx and trachea.

Because of unsuccesful L-thyroxine treatment, in August 1996 she was refered to the First Clinic of Internal Medicine, Faculty of Medicine in Bratislava. After complete general and thyroid examination she was further treated by local district physician unsing peroral L-thyroxine in a dose 300 μg daily under periodical control at the above Clinic. Since no effect of such treatment was observed on the TSH level which was repeatedly found >100.0 mU/l, various L-thyroxine brands were used including Euthyrox (Merck), Eltroxin (Glaxo) and L-Thyroxin (Berlin Chemie) and, finally, the daily dose was even increased to 500 μg of powdered tablets (Euthyrox, Merck) administered in two daily doses (300 and 200

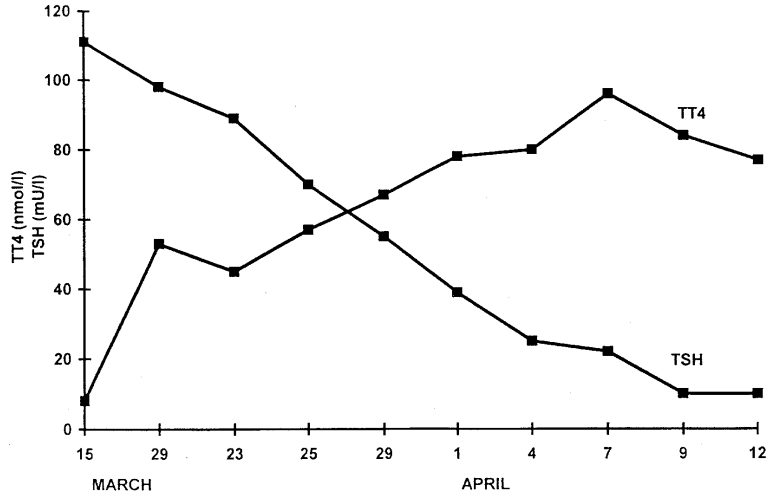

Fig. 2 Serum levels of TSH, total thyroxine (TT) and free thyroxine (FT) during 24 hours after peroral administration of powdered tablets containing 1000 mmmg of L-thyroxine (Euthyrox, Merck).

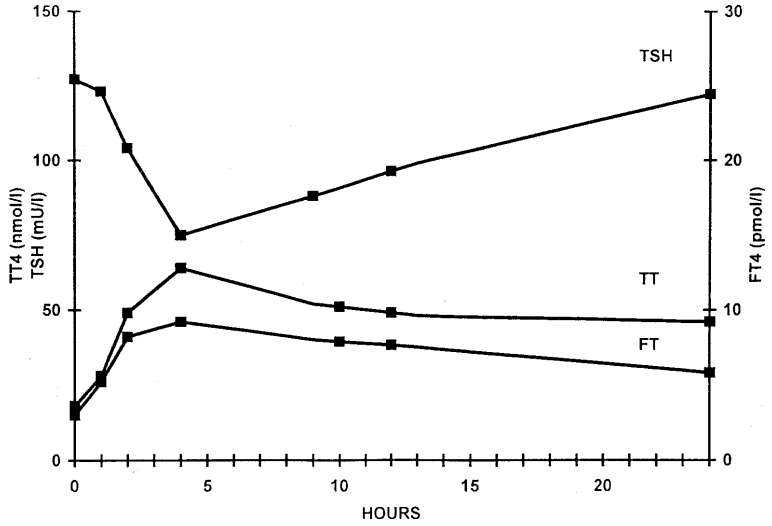

Fig. 3 Serum levels of TSH and total thyroxine (TT_4) during the four-week treatment with 500 mmmg intravenous L-thyroxine (Henning) every 3rd or 4th day for 4 weeks.

μg) between the main daily meals (i.e. at about 10.00 and 16.00 h).

General examinations: Body height 180 cm, body weight 123 kg, blood pressure 130/80 mm Hg, red blood cell sedimentation 28/85.

Pituitary computer tomography: normal finding. X-ray examination of the scull; normal sella. ECG and echocardiography: normal.

Thyroid laboratory examinations (1996): TSH 63 mU/l (repeatedly >100 mU/l – see Fig. 2 and 3); anti-TPO 10,700 U/ml; anti-TG 5200 U/ml; TSH receptor antibodies negative. Thyroxine binding antibodies ("in house" method) negative. Total T_4 and free T_4: see Fig. 2 and 3. TRH test (1996): before TRH: TSH 132 mU/l; after 20 min: TSH 306 mU/l.

Thin needle biopsy: very rare thyrocytes without any atypical signs, some colloid, peripheral blood cells (1996); hemorhagic fluid containing mostly phagocytes, lymphoplasmocytary elements, few thyrocytes without any remarkable changes (1998).

Thyroid ultrasound (1998): right lobe 10.1 ml, left lobe 12.5 ml (total volume 22.6 ml), isthmus 18 mm. Severe diffuse hypoechogenicity. Hypoechogenic nodule (9 mm diameter) in the caudal part of right lobe of 9 mm diameter.(Fig. 1)

^{131}I uptake by thyroid: 2 h: 2.5 %; 6 h: 2.8 %; 24 h: 1.3 %; 48 h: 0.6 %.

Thyroid scintigraphy with ^{99m}Te (1996): increased thyroid, suspected thyroiditis

Absorption test with peroral thyroxine (Fig. 2): Powdered tablets containing 1000 μg L-thyroxine (Euthyrox, Merck) were administered peroraly with orange juice. After 4 h TSH level decreased from 126 to 75 mU/l, while total T_4 increased from 18 to 64 nmol/l and free T_4 increased from 3.7 to 9.1 pmol/l. After 24 h the level of TSH returned to the initial value, while that of total and feee T_4 slightly but remarkably decreased. In conclusion this test showed relatively good absorption of thyroxine. Considering the body weight of 120 kg and distribution space of T_4 about 20 l (17 % of body weight), the increase of T_4 level by about 45 nmol/l means the total absorption of about 33,750 ng/l (one nmol T_4 is about 750 ng) or about 34 μg/l. From this appears that the total absorbed quantity of thyroxine was about 680 μg (i.e. 34 μg/l x 20) which is almost 70 percent of administered dose.

Treatment with intravenous thyroxine (Fig. 3): Finally, 500 μg of intravenous preparation of thyroxine (Henning, Berlin, Germany) were injected i.v. every 3rd or 4th day. After four weeks the level of TSH continuously decreased from 98 to 10 mU/l, while that of total T_4 increased from 4 to 80-100 nmol/l. This observation confirmed the appropriate decrease of pituitary TSH in response to gradualy increasing thyroxine level and, together with the previous test (Fig. 2), showed that if the intake of thyroxine would be appropriate, the patient might easily attain the euthyroid state.

Discussion

Four patients with clinical and biochemical hypothyroidism who were unsuccessfully treated with peroral thyroxine and thus suspected from malabsorption were described by Ain et al. (1991) who suggested that such patients either may be poorly compliant in taking thyroxine medication or be malabsorbing the medication. However, all patients were finally found to have normal absorption of oral thyroxine and it was suggested that such variety of factitious disorder be termed "pseudomalabsorption of levothyroxine".

Very recently (Ogawa et al. 2000) described a similar patient, 51-year-old woman, who showed persistent hypothyroidism with high TSH level, severe general fatigue and body weight gain. Replacement therapy was initiated with 150 μg thyroxine daily, which was later increased to 300 μg/day and due to persisting high TSH level and clinical symptoms of hypothyroidism even to 600 μg/day. They performed L-thyroxine loading test using levothyroxine liquid form, pulverized tablets via nasogastric tube and intravenous administration which revealed no malabsorption or metabolic disorder of levothyroxine, although oral intake of tablets was ineffective. They also reported such case as "pseudomalabsorption of levothyroxine", since the loading tests actualy showed that the absorption of L-thyroxine from g.i. tract does not seem to be impaired. The patient finaly confessed her low compliance and claimed that the inefectiveness of peroral thyroxine treatment was due to her factititous spitting out in spite of that she was carefully watched by the nursing staff or physicians from swallowing until 10 minutes thereafter.

Our patient was very similar to those reported by Ain et al. (1991) and Ogawa et al. (2000). Her poor compliance was apparently due to psychiatric disorder of depressive type which is not uncommon in severe hypothyroidism. Although she did not admit such poor compliance, it appears very likely that she took peroral thyroxine very rarely, if any. This was the case predominantly during long term periods of her stay at home between individual control examinations at the Clinic which repeatedly showed unusualy high TSH level. Actualy, for a long time she was suspected to suffer from some gastrointestinal disorder resulting in thyroxine malabsorption and from such reason she was not suspected from poor compliance until the effect of controlled peroral dose of thyroxine and of repeated intravenous thyroxine

administration (as shown above in Fig. 1 and 2) has been observed. Finally, although the reasons for regular thyroxine replacement therapy have been repeatedly explained to her and to her relatives as well to the local physician, she refused further control examinations. Currently she is living in a small village with her elderly mother. However, when contacted by phone she repeatedly claimed she is taking the medication regularly.

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BOOK REVIEW

NEUROSTEROIDS: A NEW REGULATORY FUNCTION IN THE NERVOUS SYSTERM

EDITED BY ETIENNE-EMILE BAULIEU, PAUL ROBEL, MICHAEL SCHUMACHER
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"Steroids are remarkable molecules: basically they look almost alike, being derivatives of cholesterol, but the few slight chemical differences suffice to give them the extraordinary diverse biological specificities that are important in animal physiology and medical therapeutics" – these are words of the Editors of this comprehensive and delighting monograph.

It has been known for a long time that the brain is a target organ for peripheral steroid hormones. However, in 1981 E.E. Baulieu proposed a new term "neurosteroid" which applies to such steroids which accumulate in the central and peripheral nervous system independently of the supply of peripheral endocrine glands and which can be synthesized de novo in the nervous system.

This monographs brings up to date comprehensive review on the present state of art in this new and rapidly developing field. Twenty chapters written by selected experts and carefully edited cover most of major fields of actual interest from molecular biology, biosynthesis and metabolism, mechanisms of receptor transmission and interactions with the receptors of several other neurotransmitters. The distribution of neurosteroidogenic enzymes in the central and peripheral nervous system suggests that neurosteroidogensis appears to be developmentally regulated and that the initial steps of biosynthesis are common to all steroidogenic structures. Special chapters are dealing with cytochrome P450 in CNS, with the key role of steroidogenic factor 1 in adrenal and gonadal development and in endocrine function. Of special interest are several chapters on the distribution and function of individual steroid receptors in CNS, on the neurosteroid binding sites and modulations of the action of benzodiazepine, GABA-ergic, acetylcholine, glutamate and opioid receptors by neurosteroids including either their potentiation or inhibition. Similar modulatory effects of neurosteroids were found also on neuronal voltage-gated calcium channels. From these basal findings further generate the studies on the role of neurosteroids in brain functions starting with their effects on the synaptic plasticity in the brain which is closely related to the presence and distribution of steroid receptors in the brain. Finaly, there are several observations on the effects of steroids on the developing brain, on their memory-enhancing effects and even on several pathways to the future perspectives of promising psychopharmacological profile of neurosteroids and their analogues including the considerations on their membrane and genomic effects.

This monograph will be of great to endocrinologists, biochemists, pharmacologists, neurologists, psychiatrists and all those dealing with any functions of nervous system and its integrative role.

Pavel Langer