

NOTE

Levothyroxine-Induced Liver Dysfunction in a Primary Hypothyroid Patient

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Abstract. Here we report a case of levothyroxine-induced liver dysfunction. T_4 (levothyroxine) has been more commonly used for the treatment of hypothyroidism than T_3 active hormone (triiodothyronine), because with the former drug a stabler plasma concentration is obtained after oral administration. Although there are few reports on levothyroxine-induced liver dysfunction, we treated a primary hypothyroid patient with high serum aminotransferase after administration of levothyroxine. Liver dysfunction was improved after cessation of the drug administration. Antibody to T_4 was found in the serum of the patient after this event. From clinical course and laboratory data of the patient, the episode of liver damage was considered to be induced by levothyroxine. We then administered triiodothyronine, and it did not induce liver dysfunction. Changing levothyroxine to triiodothyronine resulted in a successful clinical course in this case, as re-administration of the doubtful drug is strictly limited.

Key words: Levothyroxine, Liver dysfunction, Hypothyroid, Antibody-dependent cell-mediated cytotoxicity
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A SUPPLEMENT of exogenous thyroid hormones (dried thyroid, triiodothyronine (T_3) and levothyroxine (T_4)) has been used for the treatment of hypothyroid patients. Normally T_4 is used for hypothyroidism because of good maintenance of the active T_3 level after oral administration. It is metabolized mainly in the liver and therefore it might affect liver function, but there are rarely reports that the drug may cause liver damage [1, 2]. We treated a girl with primary hypothyroidism who had liver dysfunction after administration of levothyroxine. As the antibody to T_4 was detected in her serum after this episode, we changed from levothyroxine to triiodothyronine, which did not induce liver damage. In this case report, we describe the clinical course of

the patient in detail and review the literature on this topic.

Case Report

A 13-year-old Japanese girl with severe right coxalgia due to bilateral slipped upper femoral epiphysis underwent fixation surgery of the right head of the femur at an orthopedic hospital. As hypothyroidism was suspected, she was moved to our hospital. Her stature and weight were within or above the normal range, and her body mass index was 26.6. She had gained 5 kg in weight in two months, and had no mental retardation. Physical examination revealed dry skin without struma, and neurological findings were normal. Laboratory data routinely checked on admission to our hospital revealed the following: hemoglobin, 10.9 g/dl (normal range in our hospital; 11.3–15.2 g/dl); total cholesterol, 391 mg/dl (127–258 mg/dl); triglyceride, 247 mg/dl (40–185 mg/dl); aspartate aminotransferase (AST), 35 mU/ml (11–30

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mU/ml); alanine aminotransferase (ALT), 41 mU/ml (4–30 mU/ml); total bilirubin, 0.41 mg/dl (0.29–1.03 mg/dl); direct bilirubin, 0.05 mg/dl (0.06–0.23 mg/dl); alkaline phosphatase (ALP), 176 mU/ml (89–285 mU/ml); γ -glutamyl transpeptidase (γ -GTP), 43 mU/ml (<45 mU/ml); LDH (lactate dehydrogenase), 549 mU/ml (215–410 mU/ml); CPK (creatin phosphokinase), 216 mU/ml (19–150 mU/ml); CPK isozyme (MM), 94.6% (88–96%); CPK isozyme (MB), 2.3% (1–4%); free T₃, 0.9 pg/ml (2.47–4.34 pg/ml); free T₄, 0.10 ng/dl (0.97–1.79 ng/dl); TSH, 770 μ U/ml (0.34–3.5 μ U/ml); thyroglobulin (TG), 18 ng/ml (<30 ng/ml); thyroid stimulating (TS) antibody, 1.8 μ U/ml (<0.3 μ U/ml bovine TSH). Thyroid peroxidase (TPO) antibody, 7.9 U/ml (<0.3 U/ml); TG antibody, 11.8 U/ml (<0.3 U/ml); and TSH receptor antibody, 0.0% (<15%), were measured by radioimmuno assay (RIA) with a TPO Antibody Direct Assay kit (Cosmic Co., Tokyo, Japan), Thyroglobulin Antibody Direct Assay kit, (Cosmic Co., Tokyo, Japan), and TSH Receptor Antibody Assay kit (Cosmic Co., Tokyo, Japan), respectively. The cardiothoracic ratio in the chest X-ray was 47.4%. UCG showed a mild to moderate pericardial effusion. Abdominal

US demonstrated a slightly bright liver, diagnosed as a mild fatty liver. The enhanced cervical CT revealed an atrophic thyroid. The scintigram of the thyroid showed an irregular, suppressed uptake of ¹²³I. Aspiration biopsy of the thyroid gland was inappropriate to cytological examination as the cells obtained were not sufficient. Bone age was equivalent to that of a 12-year-old.

Since she was diagnosed as having primary hypothyroidism probably caused by Hashimoto's thyroiditis, levothyroxine sodium was administered at an initial dose of 50 μ g per day, and increased to 150 μ g. Thyroid function and the total cholesterol level were improved, but she gradually developed slight fever (37–38°C) which persisted for a couple of weeks and then general fatigue. Liver dysfunction was found at twenty-seven days after the start of levothyroxine therapy. Changes in her clinical course are shown in Fig. 1. Some of the laboratory data are shown in Table 1 and others were: hemoglobin, 11.0 g/dl; white blood cell count, 5000/mm³, with 1% eosinophils; erythrocyte sedimentation rate, 29 mm/hr (0–15 mm/hr); C-reactive protein, <0.10 mg/dl; total bilirubin, 0.47 mg/dl; direct bilirubin, 0.13 mg/dl; ALP, 629 mU/ml; γ -GTP, 34

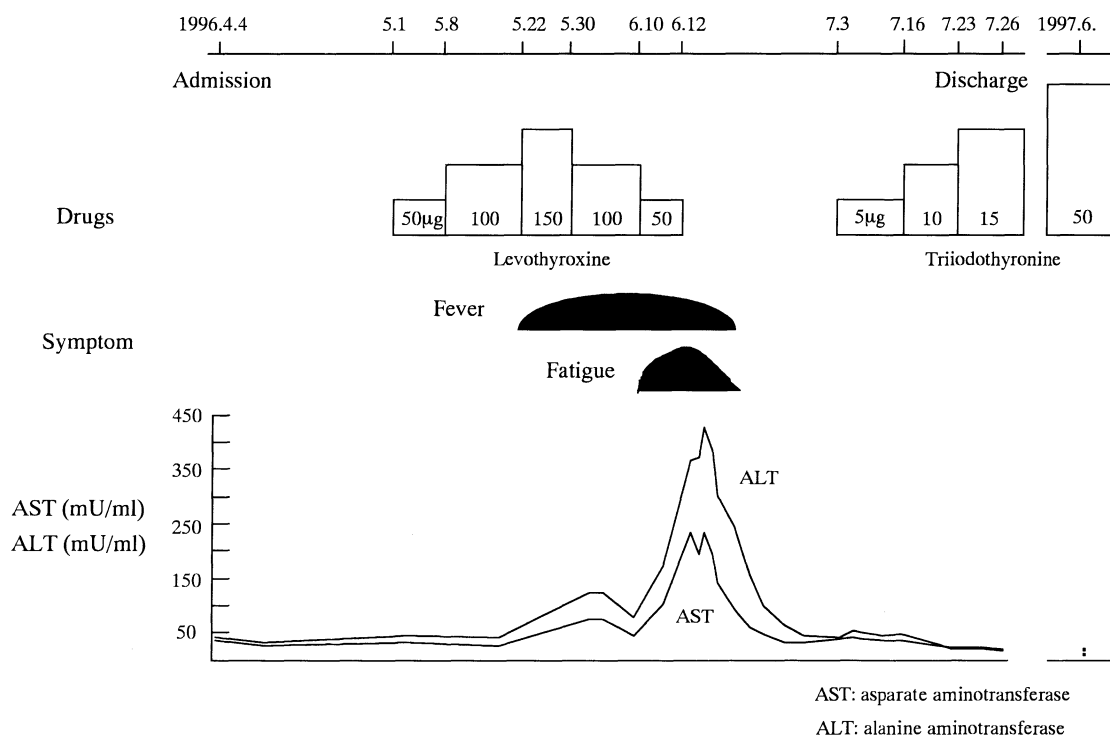


Fig. 1. Clinical course

Table 1. Changes in laboratory data

1996	4/4	4/11	5/2	5/15	6/11	6/24	7/16	7/22	7/25
AST (mU/ml)	35	24	30	27	232	33	24	23	19
ALT (mU/ml)	41	30	42	41	365	61	28	21	15
ALP (mU/ml)	176	—	171	207	629	833	566	553	—
γ -GTP (mU/ml)	43	—	30	33	—	—	27	22	—
Free T ₃ (pg/ml)	0.9	0.6	3.7	7.1	5.5	1.6	0.7	1.2	2.0
Free T ₄ (ng/dl)	<0.1	<0.1	1.06	2.10	1.11	0.15	<0.1	<0.1	0.10
TSH (μ U/ml)	770	820	81	1.9	0.6	100	600	550	6.7

mU/ml; LDH, 778 mU/ml; CPK 58 mU/ml. HA-IgM antibody, HBs antigen, HCV antibody and HDV antibody, were negative. Anti-DNA antibody, anti-mitochondrial antibody, α_1 -antitrypsin and ceruloplasmin were within normal limits. Drug-induced lymphocyte stimulation test (DLST) showed that levothyroxine was negative, but the levels of dried thyroid (T₄ plus T₃) and liothyronine sodium (T₃) were slightly higher than normal (Table 2). She took no other medication. Although DLST was negative against levothyroxine, it was strongly suspected from the clinical course that levothyroxine caused liver dysfunction (Fig. 1). Hormone therapy was discontinued on day 43th after administration. Thereafter the symptoms improved and liver function returned to normal. A radio-immunoassay method with ¹²⁵I-T₄ and ¹²⁵I-T₃ was performed to detect antibodies to levothyroxine and triiodothyronine in her serum. The results obtained showed that the ratio of binding to T₄ was slightly high (8.4%; standard level <5.0%, n=10), but that to T₃ was normal (6.0%; standard level <6.5%, n=10). No rechallenge test with levothyroxine was performed because of ethical concerns. Because she fell into

hypothyroid state again, we administered triiodothyronine at a dose of 5 μ g per day, and gradually increased the dose. She had menstruation six months after administration of triiodothyronine, and a slightly increase in the T₄ binding ratio hardly changed (7.4%). She took triiodothyronine at a dose of 50 μ g per day, and remained euthyroid and had normal liver function.

Discussion

Chronic thyroiditis, so called Hashimoto's disease, is very common in adult women and approximately 10% of those who have thyroid antibodies (antibodies to TG, TPO and TR) fall into hypothyroidism [3]. In our patient, accidental femoral fracture prompted us to suspect hypothyroidism. Low levels of free T₃ and free T₄ and high level of TSH were detected. Thyroid antibodies such as TPO, TG and TS antibody were positive, but negative in TR antibody. The cervical CT showed an atrophic thyroid. So, this case was suggestive of an autoimmune atrophic thyroiditis.

In Japan, dried thyroid, triiodothyronine, and levothyroxine have been used for hypothyroid patients, but levothyroxine has been mainly used, because it is metabolized in the tissue in an active form under an adequate level after oral administration.

There are reports that liver dysfunction induced by levothyroxine is extremely rare, and as far as we know only two cases have been published [1, 2]. The diagnosis is supported by the following findings in these two cases. Fever and liver dysfunction appeared after administration of levothyroxine, the symptom and the signs disappeared immediately

Table 2. Drug-induced lymphocyte stimulation test

Test drug	Values (cpm)	Stimulation index (%) ^{3*}
*Dried thyroid	488	202
*Liothyronine sodium	542	224
(Control)	241	
**Levothyroxine sodium	613	173
(Control)	353	

* and ** were tested at 12 and 13/Jun/1996, respectively.

^{3*} A more than 200% stimulation index was considered positive.

Table 3. Characteristics of the cases of levothyroxine-induced liver dysfunction reported in the literature

Case	Age	Sex	Treatment period	Symptom(s)	Liver functions at maximum		Eosinophilia	Reference
					AST	ALT		
1.	63	F	4 days	Fever Anorexia Fatigue	416	610	Positive	1)
2.	63	F	12 days	Fever Eruption	83	2097	Negative	2)
3.	13	F	27 days	Fever Fatigue	234	427	Negative	Our case

AST: aspartate aminotransferase (mU/ml)

ALT: alanine aminotransferase (mU/ml)

Eosinophilia means eosinophils over 5% of total peripheral leukocyte counts.

on cessation of the drug, and other causes of liver disease were unlikely. Rechallenge test by levothyroxine was positive in a Japanese case [2], and drug-induced lymphocyte stimulation test was positive in the other case [1]. These cases are summarized in Table 3, comparing them with our report. Our case showed that DLST was negative, but this finding may not be inconsistent with drug-induced liver dysfunction. Our case showed slight liver damage due to a fatty liver at admission to the hospital, but a marked increase in serum aminotransferase was observed after administration of levothyroxine. It is worthwhile mentioning that liver dysfunction was induced by exogenous administration of an endogenous hormone, levothyroxine, but not by triiodothyronine. Our case is also interesting in that we observed an increase in antibody to T₄ but not to T₃. We did not check T₄ antibody before this event, but a slight increase in the T₄ binding ratio remained 8 months after thyronine therapy.

As cell-mediated cytotoxicity is often increased in the presence of antibody [4], we did not rechallenge

with levothyroxine. Although liver is a major site of degradation of thyroid hormone, levothyroxine might induce liver damage in primary hypothyroid patients. Although levothyroxine has been easier to control than triiodothyronine, changing the former to the latter was successful in the treatment of this patient. As it is known that there are reversible cases in Hashimoto's thyroiditis [5], we are now following up the levels of hormones and antibodies to the thyroid in our patient.

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