Liver dysfunction induced by Levothyroxine Sodium Tablets (Euthyrox®) in a hypothyroid patient with Hashimoto’s thyroiditis: case report and literature review

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Abstract. A 49-year-old woman with hypothyroidism developed liver dysfunction after increasing dose of levothyroxine (L-T4) (Euthyrox®) from 25 μg to 50 μg. Viral hepatitis, autoimmune hepatitis and non-alcoholic steatohepatitis (NASH) were ruled out with examinations. She had no concurrent medication and had no history of infectious, chronic or any other autoimmune diseases. After cessation of Levothyroxine Sodium Tablets (Euthyrox®), liver enzymes gradually returned to normal. She was diagnosed levothyroxine-induced liver injury, based on criteria proposed in “Diagnosis and treatment guideline on drug-induced liver injury” issued by the Chinese Medical Association (2015). As an alternative 25 μg qod of Levothyroxine Sodium Tablets (Letrox®) was tried and increased gradually up to 75 μg daily. Since then liver enzymes have remained within normal range. The main difference of additive for both tablets is whether it contains lactose or not: Euthyrox® contains lactose which caused no liver injury, thus excluding the possibility that an additive of Euthyrox® contributed to liver injury. The relatively quicker and larger replacement with synthetic T4 for hypothyroidism inducing transient thyrotoxicosis was suspected, although thyroid function was normal. Immune-mediated drug-induced liver injury (DILI) was also not excluded. This is a rare case of drug-induced liver injury due to levothyroxine tablets. It reminded us that when replacement with synthetic T4 for hypothyroidism is done, smaller-dose initiation and slower-speed increase may be useful for treatment of cases similar to genetically susceptible individuals.

Key words: Drug-induced liver injury (DILI), Levothyroxine Sodium Tablets

HASHIMOTO’S THYROIDITIS, also known as chronic lymphocytic thyroiditis, a kind of autoimmune thyroiditis, is increasing by 5% per year in China. Hypothyroidism, mainly caused by Hashimoto’s thyroiditis, is mainly treated with replacement of thyroid hormones, especially oral administration of levothyroxine (L-T4) [1, 2]. At present, two manufacturers of levothyroxine tablets are on the market in China: Euthyrox® tablets (Merck KGaA, Germany) and Letrox® tablets (Berlin-Chemie AG, Germany) [3]. Inactive ingredients include cornstarch, gelatin, magnesium stearate, and sodium croscarmellose in both L-T4 tablets. The difference is that Euthyrox® tablets contain lactose as an additive but Letrox® tablets do not. In general, L-T4 is safe and well tolerated by patients, except for the possibility of developing osteoporosis as a result of L-T4 over-replacement, particularly in post-menopausal women, as described in the drug instructions. To our knowledge, liver dysfunction induced by administration of L-T4 has not been reported in China so far, and there are only six case reports all from Japan by searching PubMed [4-9]. Recently we encountered a female hypothyroid patient with Hashimoto’s thyroiditis, who developed liver injury due to levothyroxine (Euthyrox®).
Case Report

A 49-year-old woman had been diagnosed with Hashimoto’s thyroiditis on June 25, 2017 when her serum levels of FT4 was 9.12 pmol/L (11.5–22.7 pmol/L), FT3 was 3.4 pmol/L (3.5–6.5 pmol/L) and thyroid stimulating hormone (TSH) was 79.58 μIU/mL (0.55–4.78 μIU/mL), with normal liver function. Both antithyroglobulin antibody and antithyroid peroxidase antibody were seropositive at >500.00 IU/mL (0–60 IU/mL) and >1,300.0 IU/mL (0–60 IU/mL), respectively. Her thyroid hormone was in hypothyroidism and oral replacement therapy with 25 μg/day of L-T4 (Euthyrox®) was initiated on June 26, 2017. On July 3, 2017, 7 days later, the dosage was increased to 50 μg/day. However, at a regular visit on August 4, 2017, despite levels of FT4 (18.59 pmol/L), FT3 (4.63 pmol/L), and TSH (0.970 μIU/mL) being within normal range, she was found to have increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in blood tests, suggestive of liver dysfunction. The patient complained of fatigue and loss of appetite. Physical examination was unremarkable, and she did not have fever, jaundice, or any skin abnormality.

Laboratory findings on August 4, 2017 were as follows: white blood cells, 3.99 × 10^9/L (eosinophil 7.5%); total bilirubin, 27.2 umol/L (3.5–23.5 umol/L); AST, 1,252 IU/L (7–40 IU/L); ALT, 1,507 IU/L (13–35 IU/L); alkaline phosphatase (ALP), 85 IU/L (23–140 IU/L); gamma-GT, 28 IU/L (7–45 IU/L); and Hepatitis A virus antibody IgM, Hepatitis B virus antigen, Hepatitis B virus antibody, Hypersensitive Hepatitis C RNA quantification, Hepatitis E immunoglobulin M antibodies, Cytomegalovirus DNA quantification and Epstein-Barr virus DNA quantification were all negative. Moreover, anti-soluble liver antigen/hepatopancreatic antigen antibodies, anti-cytoplasmic liver antigen type 1 antibodies, anti-mitochondrial M2 antibody, anti-liver kidney microsomal autoantibody type 1 (LKM-1), anti-double-stranded DNA antibodies, SM, SSA and SSB were also negative. She had no history of drinking alcohol. Liver injury induced by either viral hepatitis, autoimmune hepatitis, Sjogren syndrome, systemic lupus erythematosus or non-alcoholic steatohepatitis (NASH) were excluded. Her serum levels of FT4 and FT3 were 18.59 pmol/L (11.5–22.7 pmol/L) and 4.63 pmol/L (3.5–6.5 pmol/L), respectively, and serum TSH was 0.970 μIU/mL (0.55–4.78 μIU/mL). Therefore, liver injury induced by hypothyroidism due to overdose of levothyroxine was rejected. Meanwhile, she denied having a history of chronic diseases such as hypertension, coronary heart disease, diabetes, or a history of infectious diseases such as tuberculosis and close contact history. She denied major trauma and blood transfusion history. She had no history of drug allergy, and was allergic to seafood. She did not take any other medication except L-T4 (Euthyrox®) due to Hashimoto’s thyroiditis at least in the past 90 days.

The clinical course of this case after admission is shown in Fig. 1. On August 4, 2017, administration of L-T4 (Euthyrox®) was discontinued immediately due to the suspicion that the liver dysfunction may have been due to the 50 μg tablet. On August 10, 2017, abdominal ultrasonography was performed and revealed normal results. However, serum AST and ALT were still high on the same day, 665 IU/L and 961 IU/L, respectively. Therefore, Reduced Glutathione for Injection (Atomolam) 3 g ivdrip qd + 0.9% NaCl injection 100 mL, Bicyclol Tablets (Bacenol) 50 mg po tid, Silybin Meglumine Tablets (Cilipine) 200 mg po tid were prescribed to quickly recover liver function. On August 18, 2017, liver function test results showed AST was 193 IU/L (7–40 IU/L) and ALT was 156 IU/L (13–35 IU/L) and Reduced Glutathione for Injection was discontinued considering the improvement of liver function. On September 3, 2017, FT4 was 8.96 pmol/L, FT3 was 2.72 pmol/L, TSH was 106.163 μIU/mL which showed the patient was in hypothyroid state again, and liver function showed improved test results with AST 123 IU/L (7–40 IU/L) and ALT 80 IU/L (13–35 IU/L). On September 14, 2017, AST was 104 IU/L (7–40 IU/L) and ALT was 39 IU/L (13–35 IU/L) which demonstrated the further improved liver function.

On September 18, 2017, 25 μg qod of Levothryoxine Sodium Tablets (Letrox®) was restarted with hepatic protection drugs including Bicyclol Tablets and Silybin Meglumine Tablets. On October 8, 2017, FT4 was 5.84 pmol/L, FT3 was 2.13 pmol/L, TSH was 150 μIU/mL, still in hypothyroidism, and L-T4 (Letrox®) was carefully increased up to 25 μg qd. On November 3, 2017, L-T4 (Letrox®) was increased up to 50 μg qd. On November 22, 2017, AST and ALT was within normal range and drugs to protect the liver including Bicyclol Tablets and Silybin Meglumine Tablets were discontinued. At the same time, FT4 was 12.5 pmol/L, FT3 was 3.55 pmol/L, TSH was 54.42 μIU/mL and L-T4 (Letrox®) was carefully increased up to 75 μg qd. The patient was followed up since then and L-T4 dosage was adjusted according to her thyroid function.

On June 12, 2018, her serum levels of FT4 and FT3 were 19.37 pmol/L and 3.41 pmol/L, and serum TSH was 3.65 μIU/mL, showing the thyroid function was in the normal range with 75 μg daily of L-T4 (Letrox®). There has been no recurrence of liver dysfunction. The patient was followed up to January 4, 2019 and the thyroid and liver function findings were always within normal range with 75 μg daily of L-T4 (Letrox®). We
suspect these transient liver biochemical abnormalities were related to the quickly increased thyroid hormone in the hypothyroid patient which was similar to transient thyrotoxicosis and impaired liver function.

**Discussion**

In general, L-T4 is safe and well tolerated by patients at normal dosage. To date and to our knowledge, there has been only six case reports of liver dysfunction induced by administration of L-T4 in a literature search, which are presented in Table 1 [4-9]. Drug-induced hepatotoxicity remains a diagnosis of exclusion. In the present case, according to “Diagnosis and treatment guideline on drug-induced liver injury” issued by the Chinese Medical Association (2015), several factors are able to potentiate the diagnosis of L-T4-induced hepatotoxicity, including timing of drug intake, clinical course of liver injury, and exclusion of other causes of liver injury. When the Roussel Uclaf Causality Assessment Method (RUCAM) scale was applied to our patient, the assessed score was consistent with probable drug-induced liver injury (DILI) (Table 2) [10]. Therefore, we concluded that liver injury in our case was probably caused by administration of L-T4 (Euthyrox®).

According to the L-T4 (Euthyrox®) instructions, T4 is slowly eliminated. The major pathway of thyroid hormone metabolism is through sequential deiodination. Approximately 80% of circulating T3 is derived from peripheral T4 by monodeiodination. The liver is the major site of degradation for both T4 and T3. Approximately 80% of the daily dose of T4 is deiodinated to yield equal amounts of T3 and reverse T3 (rT3). T3 and rT3 are further deiodinated to diiodothyronine. Thyroid hormones are also metabolized via conjugation with glucuronides and sulfates and excreted directly into the bile and gut where they undergo enterohepatic recirculation. García-Cortés et al. demonstrated that different risk factors have been associated to the development of DILI including host factors, drug-dependent factors, and environmental conditions [11]. Among drug-dependent risk factors, daily dose greater than 50 mg, more than 50% of hepatic metabolism, greater lipophilicity, and/or dual inhibition of mitochondrial and bile salt export pump.
<table>
<thead>
<tr>
<th>First author</th>
<th>Patient’s sex</th>
<th>Patient’s age</th>
<th>Initial diagnosis</th>
<th>Symptoms of liver injury</th>
<th>Liver functions at maximum and the corresponding thyroid function</th>
<th>Initial drugs</th>
<th>Final drugs</th>
<th>Treatment process after liver injury</th>
<th>Probable causes of liver injury</th>
<th>Country</th>
<th>Publication year</th>
<th>Language</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kang S [4]</td>
<td>Female</td>
<td>54</td>
<td>Subclinical hypothyroidism</td>
<td>No fever, jaundice, or any skin abnormality</td>
<td>AST 269 IU/L, ALT 233 IU/L, ALP 395 IU/L; FT3 2.46 μg/dL, FT4 1.24 ng/dL, Normal</td>
<td>L-T4 tablet</td>
<td>L-T4 powder</td>
<td>L-T4 tablet was discontinued. Four years after L-T4 cessation, L-T4 powder was increased at a rate of 50-80-50-μg daily and stopped because of liver dysfunction; 25 μg L-T4 powder was restarted and was carefully increased at a rate of 30-40-50-60-70 μg daily without liver dysfunction.</td>
<td>An additive in the L-T4 tablet</td>
<td>Japan, Kobe</td>
<td>2015</td>
<td>English</td>
</tr>
<tr>
<td>Kawakami T [5]</td>
<td>Male</td>
<td>63</td>
<td>Primary hypothyroidism</td>
<td>No jaundice</td>
<td>AST 670 IU/L, ALT 884 IU/L, ALP 458 IU/L; FT3 2.5 μg/mL, FT4 0.8 ng/dL, normal, serum TSH 150.6 μIU/mL, high</td>
<td>L-T4</td>
<td>T3</td>
<td>L-T4 was discontinued. Dried thyroid powder (T3 + T4) was administered, but ALT still elevated and jaundice developed. Then liothyronine (T3) was used instead of T4 and discontinued because of exacerbated total bilirubin and jaundice. About four months later, T3 was ceased and no liver injury occurred.</td>
<td>A complex of L-T4 and carrier protein may be easily recognized by immune system in genetically susceptible individuals, leading to liver injury.</td>
<td>Japan, Tokyo</td>
<td>2007</td>
<td>English</td>
</tr>
<tr>
<td>Ohmon M [6]</td>
<td>Female</td>
<td>13</td>
<td>Primary hypothyroidism probably caused by Hashimoto’s thyroiditis</td>
<td>Fever (37–38°C), general fatigue</td>
<td>AST 232 IU/L, and ALT 365 IU/L, ALP 629 IU/L; FT3 5.5 μg/mL, high, FT4 1.11 ng/dL, TSH 0.6 μIU/mL, high</td>
<td>L-T4</td>
<td>T3</td>
<td>L-T4 was discontinued. T3 was gradually increased at a dose of 5-10-15-50 μg per day without liver dysfunction.</td>
<td>Liver is a major site of degradation of thyroid hormone and L-T4 might induce liver damage in primary hypothyroid patients.</td>
<td>Japan, Tochigi</td>
<td>1999</td>
<td>English</td>
</tr>
<tr>
<td>Shibata H [7]</td>
<td>Female</td>
<td>63</td>
<td>Hypothyroidism with Hashimoto’s thyroiditis</td>
<td>General malaise</td>
<td>AST 704 IU/L, ALT 1044 IU/L</td>
<td>T3, L-T4</td>
<td>T3</td>
<td>T3 was discontinued. L-T4, 25 μg per day for four days and liver injury occurred. For the following four months no medication was taken. Then T3 was administered with a dose of 5 μg per day, increased gradually up to a daily dose of 35 μg without liver dysfunction.</td>
<td>Hypersensitivity induced by exogenous administration of T3, L-T4 and desensitization to T3 at last</td>
<td>Japan, Tokyo</td>
<td>1986</td>
<td>English</td>
</tr>
<tr>
<td>Our case</td>
<td>Female</td>
<td>49</td>
<td>Hypothyroidism with Hashimoto’s thyroiditis</td>
<td>Fatigued, anorectic</td>
<td>AST 1.252 IU/L, ALT 1.507 IU/L, ALP 85 IU/L; FT4 18.59 pmol/L, FT3 4.63 pmol/L, TSH 0.970 μIU/mL, normal</td>
<td>L-T4 (Euthyrox®)</td>
<td>L-T4 (Letrox®)</td>
<td>L-T4 (Euthyrox®) was discontinued. 45 days later, L-T4 (Letrox®) was gradually increased at a dose of 12.5-25-50-75 μg daily no liver injury occurred.</td>
<td>The larger initial dose and the faster increased dose resulted to oxidative stress, and mitochondrial dysfunction of liver and liver injury occurred in genetically susceptible individuals.</td>
<td>China, Jinan</td>
<td>2019</td>
<td>English</td>
</tr>
</tbody>
</table>

*“—”: Inui A [8] and Toki M [9] were published in Japanese and detailed information was not obtained.*
(BSEP) are properties of the drug that can contribute to a risk for idiosyncratic DILI [12-16]. As the major site of metabolism for both T4 and T3 is the liver, this brings a possibility of liver damage. Mosedale and Watkins reviewed the key components that lead to DILI, including oxidative stress, mitochondrial dysfunction and changes within bile acid homeostasis [17]. The present patient had signs of hypothyroidism and the relatively quicker and larger replacement with synthetic T4 increased the oxygen demand on hepatocytes, which could increase reactive oxygen species (ROS) accumulation. When the processes that exist to regulate cellular levels of ROS are exceeded, oxidative stress can result in damage to critical cellular components and eventually cell death. Additionally, the possibility was not excluded that L-T4, as a hapten protein forming covalent adducts, was taken up by antigen-presenting cells or stimulated the production of danger signals, hence triggering a pathogenic adaptive immune response and leading to immune-mediated DILI [18]. To our knowledge, only a few patients have experienced L-T4-induced liver injury, and so genetic factors, associated with individual risk of developing liver injury on exposure to medications, may alter the nature or the magnitude of immune-mediated liver injury and increase the likelihood of DILI in susceptible individuals [18].

The concentration of thyroid hormones in tissues is regulated by deiodinases and thyroid hormone transporters. Deiodinase enzyme isoforms (DIO1, DIO2, and DIO3) mainly control intracellular thyroid hormone concentrations. DIO enzymes convert T4 to biologically active T3. Activities of DIO1 and DIO2 play a pivotal role in the negative feedback regulation of pituitary TSH secretion [19, 20]. The DIO2 activity in the rs225104 TT genotype was higher than that in the CC genotype [21]. Arici et al. reported it should be given in lower dose to the patients with rs225014 TT and rs225015 GG genotypes in DIO2 in order to provide proper treatment with higher effectivity and lower toxicity [22]. Uridine diphosphate glucuronosyltransferases (UGTs) are responsible for T4 metabolism in human liver as thyroxine glucuronide. Two common UGT1A subfamily enzymes, UGT1A1 and UGT1A3, provide T4 glucuronidation in humans [23]. UGT1A1 has a higher affinity than UGT1A3 for T4 in T4 glucuronidation while UGT1A3 has a higher capacity for T4 glucuronidation. It was reported that there is a significant correlation between UGT1A1*28 and T4 glucuronidation [24]. Yoder Graber et al. pointed out that hypothyroid patients with homozygous UGT1A1*28 variant should receive a lower L-T4 dose [24]. Therefore, our present case may have the rs225104 TT genotype or rs225015 GG genotypes in DIO2 or homozygous UGT1A1*28 variant. Liu et al. suggested single nucleotide polymorphisms (SNP) mutations coded in thyroid hormone receptor (THR) influenced individual susceptibility to triiodothyronine [25]. Therefore, the balance of thyroid hormones in human is affected by multiple gene loci and gene polymorphism.

In the six published case reports, three of which in the English literature on liver injury was suspected allergic reactions to L-T4 itself [5-7]. Drug-induced lymphocyte stimulation test (DLST) was performed, but two of the reported cases showed negative response to L-T4 [5, 6] and the remaining one showed positive results for both L-T4 and T3 [7]. Therefore, the statement that the mechanism of liver injury is hypersensitivity induced by exogenous administration of L-T4 will need to be further clarified. There are two case reports in the Japanese literature of liver injury suspected due to L-T4 [8, 9]. Inui et

### Table 2  Patient’s score on the Roussel Uclaf Causality Assessment Method scale

<table>
<thead>
<tr>
<th>Variable</th>
<th>Clinical results</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver injury type</td>
<td>Hepatocellular</td>
<td></td>
</tr>
<tr>
<td>Time of onset of the event</td>
<td>First exposure</td>
<td></td>
</tr>
<tr>
<td>Time from drug intake until reaction onset</td>
<td>5–90 days</td>
<td>+2</td>
</tr>
<tr>
<td>Course of reaction</td>
<td>ALT descending by ≥50% in 30 days</td>
<td>+2</td>
</tr>
<tr>
<td>Alcohol or pregnancy</td>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;55 years</td>
<td>0</td>
</tr>
<tr>
<td>Concomitant therapy</td>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Exclusion of non-drug-related causes</td>
<td>Ruled out</td>
<td>+2</td>
</tr>
<tr>
<td>Previous information on hepatotoxicity</td>
<td>Reaction published but unlabeled</td>
<td>+1</td>
</tr>
<tr>
<td>Response to re-administration</td>
<td>Not available</td>
<td>0</td>
</tr>
<tr>
<td>Total score</td>
<td>Probable</td>
<td>7</td>
</tr>
</tbody>
</table>

Levothyroxine induced liver dysfunction

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al. reported a case of allergic hepatitis although the cause of allergy was not clarified [8]. Toki et al. reported a case of liver dysfunction due to Fe₂O₃ of Thyradin-S® [9]. In 2015, Kang et al. presented a case report of liver dysfunction due to some additive other than Fe₂O₃ in L-T4 tablet form [4]. In all the above literature, four showed the mechanism of liver injury is hypersensitivity [5-8] and two showed the additive in the L-T4 tablet induced liver dysfunction [4, 9]. By reading the above English literature carefully, we knew that the treatment process after liver injury was as follows: discontinue L-T4 tablet firstly, and then a few months or years later, restart 25 μg L-T4 powder [4] or 5 μg T3 [6, 7] and carefully increase up to the proper dosage at a very slow rate without liver dysfunction, which may be a way of drug desensitization or induced immune tolerance of the body.

Taking into account the above factors, after 45 days discontinuation of L-T4 (Euthyrox®), 12.5 μg daily L-T4 (Letrox®) was restarted and gradually increased up to 75 μg daily, and no liver injury recurred. The difference is that Euthyrox® tablets contain lactose as an additive which generally causes no liver dysfunction but Letrox® tablets do not contain. Therefore, this excluded the possibility that an additive of Euthyrox® contributed to liver injury. We suspect that the relatively quicker and larger replacement with synthetic T4 for hypothyroidism induced transient thyrotoxicosis and impaired liver function in genetically susceptible individuals, although the thyroid function of the patient was within normal range. Of course, the possibility of immune-mediated DILI due to L-T4 was not excluded. As is well known, hyperthyroidism could cause liver injury. However, liver dysfunction also occurred in those with normal thyroid function as shown in the present patient and in the previous literature [4, 26]. Duong et al. reported a case of acute mixed liver injury due to hypothyroidism [27]. These cases remind us that the safe dose range of thyroid hormone is narrow, and that a stable and normal state of thyroid function is critical for human health.

In conclusion, we reported a case with levothyroxine-induced liver injury suspected to be due to the relatively quicker and larger replacement with synthetic T4 for hypothyroidism inducing transient thyrotoxicosis, although the patient had normal thyroid function. The present case should remind us that when replacement with synthetic T4 for hypothyroidism is done, smaller-dose initiation and slower-speed increase should be considered to the genetically susceptible individuals.

Disclosure

None of the authors have any potential conflicts of interest associated with this research.

References


