Pseudomalabsorption of Levothyroxine: A Case Report

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Abstract. A 51-year-old woman who had been treated with levothyroxine sodium because of hypothyroidism after total thyroidectomy for thyroidal cancer was admitted to our hospital for persistent hypothyroidism despite large dose administration of levothyroxine (600 μ g/day). The patient complained of severe general fatigue and body weight gain. Free thyroxine, free triiodothyronine and thyrotropin levels were 0.97 ng/dl, 1.55 pg/ml and 24.51 μ U/ml, respectively, under oral administration of levothyroxine. Levothyroxine loading test performed by liquid form, pulverized tablets via nasogastric tube and intravenous administration revealed no evidence of malabsorption or metabolic disorder of levothyroxine, although oral intake of tablets was ineffective due to her factitiousness. We report here a possible case of “pseudomalabsorption of levothyroxine” to emphasize the clinical recognition of this disorder in patients with resistant hypothyroidism.

Key Words: Thyroid carcinoma, Hypothyroidism, Munchausen syndrome

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LEVOTHYROXINE sodium is the most commonly used thyroid hormone preparation for the treatment of hypothyroidism. Evaluation of the current levothyroxine formulation shows a mean daily replacement dose of $112 \pm 19 \mu\text{g}$ ($1.63 \pm 0.42 \mu\text{g/kg}$ body weight) and absorption from the gastrointestinal tract at approximately 81% of the administered oral dose [1]. However, it has been reported that a high dose of levothyroxine is required for maintenance of euthyroid state in several patients with hypothyroidism and that some of these are levothyroxine resistant [2]. The issue is whether this is a case of poor compliance in taking levothyroxine or a case of malabsorption of the medication. Ain and his colleagues [2] evaluated four patients with hypothyroidism despite therapy with up to eightfold the mean daily dose of levothyroxine, and revealed

that all patients had normal absorption of oral levothyroxine and that their persistent condition was due to noncompliance with levothyroxine. They suggested that latent psychiatric factors may result in noncompliance with intent to deceive and termed this variety of factitious disorder “pseudomalabsorption of levothyroxine”.

We present here a case of persistent hypothyroidism despite large dose administration of levothyroxine. To determine the cause of levothyroxine resistance in this patient, we applied the drug through various routes and measured levothyroxine absorption using nonisotope method. These studies showed normal absorption of levothyroxine, suggesting that the patient was a rare case of hypothyroidism due to pseudomalabsorption of levothyroxine [2].

Case Report

A 51-year-old woman was admitted to our hospital on September 30, 1998, because of persistent hypothyroidism despite large dose administration of

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levothyroxine sodium (Tyradin S®). Her past history was negative except for cholelithiasis and thyroidectomy. In 1996, she noticed thyroid nodules, which were later diagnosed pathologically as papillary carcinoma of the thyroid. Total thyroidectomy including excision of four portions of the parathyroid gland followed by irradiation of the neck were performed. Replacement therapy commenced with 150 µg of levothyroxine daily, which was increased to 300 µg/day when persistent hypothyroidism was noticed associated with high thyrotropin (TSH) levels (40 µU/ml; normal, 0.33 to 4.05 µU/ml) and severe generalized fatigue. Calcium lactate and vitamin D were also administered for postoperative hypoparathyroidism. To avoid the interference with levothyroxine absorption, other medication was completely excluded. In July 1998, hypothyroidism progressed despite use of incremental doses of levothyroxine. Persistently low thyroxine (T4) levels and high TSH levels were noted, despite self-report of excellent compliance with the prescribed thyroid hormone medication. Persistence of symptoms necessitated a further increase of levothyroxine to 600 µg/day, although the serum free triiodothyronine (FT3) level was <0.7 pg/ml (normal, 1.71 to 3.71 pg/ml), free thyroxine (FT4) level <0.2 ng/dl (normal, 0.97 to 1.69 ng/dl), and TSH level of 159.8 µU/ml.

On admission, the patient weighed 78.4 kg, and was 156.2 cm tall. She was afebrile (body temperature, 36.6°C), blood pressure was 128/88 mmHg with a regular pulse rate of 78 beats/min. The

patient complained of general fatigue and numbness of fingers on both hands, but was mentally alert with good intellect. Chest examination was unremarkable. Both achilles and patellar jerks were normal. Her medical history was not significant for medical, psychiatric, or surgical interventions. Routine laboratory tests were normal except for mild hypocalcemia. The results of thyroid function tests on admission are shown in Table 1. She had hypothyroidism, together with low levels of parathyroid hormone and vitamin D. Anti-thyroglobulin and anti-microsomal antibodies were positive but anti-T3 and anti-T4 antibodies were negative. Fecal fat excretion was normal. Chest and abdominal roentgenograms were normal. Gastrointestinal endoscopy was unremarkable and examination of biopsy materials from the stomach, duodenum, small-bowel and rectum showed no histopathological abnormalities.

The clinical course is summarized in Fig. 1. On admission, thyroid function was transiently normalized with replacement of levothyroxine (600 µg/day). However, hypothyroidism gradually progressed despite the intake of 600 µg/day of levothyroxine. With the suspicion of malabsorption, levothyroxine treatment was switched from oral to rectal route using levothyroxine suppositories [50 µg of levothyroxine was dissolved with 75 mg of two kinds of witepsol (E-75 and H-15)]. The patient tried to use the suppositories several times, but she finally declined this form of treatment for the reason that

Table 1. Thyroid function tests on Admission

T3	0.73	ng/ml	(0.69–1.46)
T4	9.84	µg/dl	(6.48–12.73)
FT3	1.55	pg/ml	(1.71–3.71)
FT4	0.97	ng/dl	(0.97–1.69)
TSH	24.51	µU/ml	(0.33–4.05)
rT3	187	pg/ml	(190–375)
TBG	29.7	µg/ml	(12.0–30.0)
Tg	≤5.0	ng/ml	(0–30)
Anti-TPO antibody	1.4	U/ml	(0–0.3)
Anti-Tg antibody	1.3	U/ml	(0–0.3)
TBII	–3.00	mlU/ml	(<15)
Anti-T3 antibody	(–)		(–)
Anti-T4 antibody	(–)		(–)

T3, triiodothyronine; T4, thyroxine; FT3, free triiodothyronine; FT4, free thyroxine; rT3, reverse triiodothyronine; TPO, thyroid peroxidase; Tg, thyroglobulin; TBII, thyroxine binding inhibitory immunoglobulin

Fig. 1. Clinical course. After admission, hypothyroidism persisted despite confirmed intake of 600 $\mu\text{g/day}$ of levothyroxine. In November 1998, the patient was treated with 600 μg of levothyroxine combined with 150 μg of liothyronine daily. However, because of persistent hypothyroidism, levothyroxine (200 $\mu\text{g/day}$) was administered intravenously which resulted in improvement of her condition. After the cessation of intravenous administration in January 1999, hypothyroidism recurred despite increases in the dose of levothyroxine to 900 $\mu\text{g/day}$. Levothyroxine loading test was performed in February 1999, which was followed by replacement therapy with 150 μg of levothyroxine.

she could not endure its discomfort. In November, she was treated with 600 μg levothyroxine combined with 150 μg of liothyronine daily, but the level of FT4 remained low at 0.11 ng/dl, as was the level of T4 (1.04 $\mu\text{g/dl}$, normal, 5.00 to 12.50 $\mu\text{g/dl}$), and TSH level was greater than 200 $\mu\text{U/ml}$. Suspecting low compliance to oral medication, she was carefully watched by the nursing staff or physicians at her bedside or the staff's room from swallowing until 10 min thereafter, but it did not correct her condition. We then prepared a solution of levothyroxine 50 $\mu\text{g/ml}$ for intravenous administration [5 mg of levothyroxine dissolved in 1 ml of 0.1 N NaOH was diluted with distilled water, totalling 100 ml, and sterilized with membrane filter]. First, the serial change of serum T4 level was examined after the intravenous administration of 100 μg of levothyroxine (Fig. 2D). She was then administered levothyroxine intravenously using a dose of 200 $\mu\text{g/day}$. This resulted in the correction of serum TSH level to

20 $\mu\text{U/ml}$ and a gradual improvement of hypothyroidism during continued treatment with 200 $\mu\text{g/day}$ of intravenous levothyroxine culminating in a state of euthyroidism. Cessation of intravenous levothyroxine resulted in recurrence of hypothyroidism with serum T4 level of 7.06 $\mu\text{g/dl}$, FT4 level of 0.78 ng/dl, and TSH level of 51.83 $\mu\text{U/ml}$, despite further increase in oral levothyroxine dose to 900 $\mu\text{g/day}$.

A thyroid hormone loading test was then performed (Fig. 2). A series of study was performed after informed consent was obtained. The patient received 1,000 μg (1,250 nmol) of levothyroxine in the form of twenty 50 μg -tablets as a single loading dose (Fig. 2A). Two weeks after, she received 1,000 μg of levothyroxine in a liquid form (Fig. 2B). Ingestion was verified by careful observation from intake until 30 minutes later. Two weeks after that, the patient also consented to the placement of a nasogastric tube for instillation of crushed

Fig. 2. Levothyroxine loading test. Note the increment in serum T4 level after levothyroxine loading by the following routes: A) tablet (1,000 μ g), B) liquid form (1,000 μ g), C) nasogastric tube of pulverized tablet (1,000 μ g) and D) intravenous administration (100 μ g). Later, by the patient's own confession, it was clarified that the ineffectiveness of the tablet form (A) was due to her factitious spitting out.

levothyroxine tablets (Fig. 2C). Serial blood samples were obtained for hormone assays, before and after the administration of levothyroxine, for up to 24 hours [3]. Since the T4 distribution volume is approximately 12 L (10%, 13.4% to 14.0% of body weight) [4, 5], 10% of each absorbed dose is expected to produce a 10.4 nmol/l increment increase in serum T4. In the study using the tablet form, the observed rise in serum T4 levels showed less than 10% absorption of the tablet (Fig. 2A). A peak increment of 120 nmol/l was found in the liquid study, showing nearly 100% absorption of the oral dose (Fig. 2B). On examination using 1,000 μ g of pulverized levothyroxine tablets and nasogastric tube, the increment increase in serum level of T4 indicated 100% absorption of the ingested levothyroxine (Fig. 2C). The patient admitted her poor compliance and also complained of difficulty taking the tablets. Replace-

ment therapy was continued using 150 μ g oral levothyroxine, but her thyroid condition was still unstable. The patient is being followed up and is also being examined by psychiatrists.

Discussion

It is rare to encounter patients in a state of clinical or biochemical hypothyroidism who are being treated with high dose levothyroxine. Ain *et al.* [2] measured thyroid hormone levels after a loading dose of levothyroxine in such patients and showed that all patients were ultimately found to have normal absorption of oral levothyroxine. These patients can be distinguished from those with simple noncompliance in that they exhibit characteristics of a factitious disorder. Ain *et al.* [2] labeled this variety

of factitious disorder "pseudomalabsorption of levothyroxine" [2]. Psychiatric disorders are common in hypothyroid patients, and are usually of the paranoid or depressive type and may induce agitation, i.e., myxedema madness [6, 7]. It is unclear whether pseudomalabsorption is a specific manifestation in hypothyroidism, since the incidence of pseudomalabsorption in hypothyroidism is unknown. The alternative diagnosis of our case is a variant of Munchausen syndrome characterized as an acute illness with dramatically false history or self-inflicted illness [8].

Oral levothyroxine is the first choice of replacement therapy for patients with hypothyroidism. In most hypothyroid adults, an average dosage of $1.6 \mu\text{g}/\text{kg}$ of body weight per day should normalize serum TSH levels, an average dosage of $2.0 \mu\text{g}/\text{kg}$ of body weight per day being required to suppress TSH [1, 9]. Typically, 70 to 80% of an orally administered dose of levothyroxine is absorbed by the gastrointestinal tract [1, 10], but the mechanism of translocation across the mucosa remains unclear [11, 12]. Levothyroxine absorption is probably the greatest from the ileum under normal circumstances, and is enhanced by fasting [2]. Levothyroxine malabsorption is observed after jejunoileal bypass procedures, as well as in short bowel syndrome, severe hepatic cirrhosis, congestive heart failure, and possibly in the presence of serum anti-T4 antibodies [2]. Several commonly used drugs may also impair the intestinal absorption of levothyroxine, such as aluminum hydroxide [13], sucralfate [14], lovastatin [15], ferrous sulfate [16] and cholestyramine [17]. Such drug-induced malabsorption may potentially increase the levothyroxine dose requirement. When it appears likely that levothyroxine has been reliably ingested, factors affecting absorption should be considered. In the present case, none of the above-mentioned factors potentially interfering with levothyroxine absorption was applicable.

The catabolism of intravenously administered levothyroxine was not enhanced in this patient. We further investigated possible malabsorption of levothyroxine in our patient. Oral administration of $1,000 \mu\text{g}$ of levothyroxine in tablet form resulted in minimal incremental increases in serum T4 levels. However, normal absorption of levothyroxine was noted when the drug was used in liquid form and in direct administration via nasogastric tube. The

difference in incremental increase in absorption between tablets (we ensured the patient took the tablets) and liquid by direct measurement of levothyroxine was more than tenfold. As reported previously [18–20], peak absorption occurred 2 to 4 hours after levothyroxine administration at 82 to 100% of the administered dose in both our liquid and nasogastric studies. As for the turnover of levothyroxine, evaluation of T4 levels showed normal levels under intravenous administration of levothyroxine (Fig. 2). Normal absorption and metabolism were thus demonstrated in these loading tests, suggesting that persistent hypothyroidism might be due to poor compliance. Indirect observation indicated the patient took her medication and there was no evidence of spitting out. It is considered that oral administration using the liquid form is very difficult to spit out compared to tablet form. The associated hypocalcemia might also be due to not taking vitamin D and calcium lactate. Once levothyroxine was injected intravenously, the patient became euthyroid. However, since the euthyroid state restored by intravenous replacement did not affect the patient's attitude to oral intake, her factitious behavior was not attributable to her hypothyroidism. Our case is rather to be classified as a factitious disorder, representing noncompliance with intake of medication and such noncompliance in this case is likely to be based on a psychiatric background. Thus, management of this disorder only by using high dose thyroid hormone replacement therapy is inadequate. Levothyroxine therapy administered through different routes (oral, rectal, intravenous, and intramuscular) should be performed in order to establish the possible presence of this disorder.

In summary, we report a rare case of pseudomalabsorption of levothyroxine. Patients presenting with hypothyroidism post-thyroidectomy despite high dose of levothyroxine replacement therapy should be suspected of having this disorder. However, the condition is difficult to diagnose as pseudomalabsorption of levothyroxine because of patients' behavior and psychiatric condition. Differences in absorption between tablet and liquid forms of levothyroxine may help establish the correct diagnosis. Special care should be given to the mental status of these patients. The daily dose of levothyroxine should be reduced with increasing compliance to avoid unexpected thyrotoxicosis.

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