

A curious case of refractory hypothyroidism due to selective malabsorption of oral thyroxine

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ABSTRACT

There are very few cases in the literature in which refractory persistent hypothyroidism responded only to parenteral doses of levothyroxine and no evidence of any malabsorptive disorder could be identified. Here, we present a rare case of a 35-year-old woman with refractory hypothyroidism who responded only to intravenous doses of levothyroxine. We also discuss possible causes for the same.

Key words: Refractory hypothyroidism, selective malabsorption, thyroxine

INTRODUCTION

Oral levothyroxine sodium (LT₄) remains the mainstay of treatment of hypothyroidism to achieve physiological thyroid hormone levels. The mean treatment dosage is 1.6 µg/kg bodyweight per day.^[1] Intestinal absorption ranges from 70% to 80% of the administered dose and it differs from patient to patient.^[2] In addition, absorption is higher in the fasting state. However, hypothyroidism persists and euthyroid state cannot be achieved in a few cases even after supplementing adequate or excessive doses of oral thyroxine. In such cases of refractory hypothyroidism, the main differentials to be considered are (a) poor patient compliance to oral thyroxine, (b) deiodinase deficiency, and (c) various malabsorption disorders. Of these poor compliance is very commonly seen in refractory hypothyroidism.^[3-5] There are very few cases in the literature in which refractory persistent hypothyroidism responded only to parenteral doses of levothyroxine and no evidence of any malabsorptive disorder could be identified.

Here, we present a rare case of a 35-year-old woman with refractory hypothyroidism who responded only to intravenous doses of levothyroxine. We also discuss possible causes for the same.

CASE REPORT

A 35-year-old female presented to the physician with complaints of gradual increase in weight, loss of appetite, lethargy, and weakness over the past 4 years. On examination, she had dry scaly skin, peripheral edema, and a blood pressure of 140/100 mm Hg. She was incidentally diagnosed to be hypothyroid during her third pregnancy and treatment started on 100 µg thyroxine 4 years ago. The delivery was uneventful and the baby also had normal thyroid profile. Her symptoms gradually worsened and her thyroid-stimulating hormone (TSH) levels reached 651.4 µIU/ml 1 year ago. The dose of thyroxine was gradually increased upto 400 µg/day. Patient was compliant to the intake of thyroxine. Repeated thyroid profiles on thyroxine doses between 100 and 400 µg showed TSH ranging from 270 to 360 µIU/ml. Her free T₃ and free T₄ were also very low. Oral intake under physician supervision did not help. Her serum cholesterol was elevated upto 338 mg/dl. The patient was additionally administered 25 µg of triiodothyronine twice daily. Even after such a high dose of T₄ and addition of oral T₃, her serum T₃, T₄, and TSH did not normalize. She was thoroughly investigated for refractory primary hypothyroidism. Her antithyroglobulin antibody level was 261 IU/ml and anti-TPO antibody was 974 IU/

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ml. Family history of hypothyroidism was present.^{99mTc} pertechnetate thyroid scan showed normally located thyroid gland with normal homogenous tracer uptake in both the lobes of thyroid gland.

As a next step, malabsorption of oral thyroxine was kept as one of the differential diagnosis. Although there was no history of diarrhea/steatorrhea or other clinical findings of malabsorption, further investigations to rule out malabsorption as a cause were done. Hemogram did not reveal anemia and peripheral smear was normal. Stool examination was normal. Upper gastrointestinal (GI) endoscopy was done which was also normal. Duodenal biopsy was taken and it did not show pathological abnormalities consistent with malabsorptive disorder [Figure 1]. Antibodies to gliadin and transglutaminase were in normal range. Her D-xylose test was done which was also within normal limits, i.e., 4 mmol/L. We tried supplementation of thyroxine by intravenous route. Injection levothyroxine (LT₄) 200 µg once in 3 days was started. After five doses of Levothyroxine, her TSH levels started improving and reached 68 µIU/ml. We continued with the doses of intravenous levothyroxine and after five more doses her TSH levels reached 28 µIU/ml with normalization of T3 and T4 levels. On stopping, the intravenous thyroxine and maintaining the patient on oral medication, the TSH started rising again with fall in T3 and T4 levels within 7 days. This provided us with evidence of oral malabsorption of thyroxine.

DISCUSSION

Primary hypothyroidism can be clearly demonstrated by

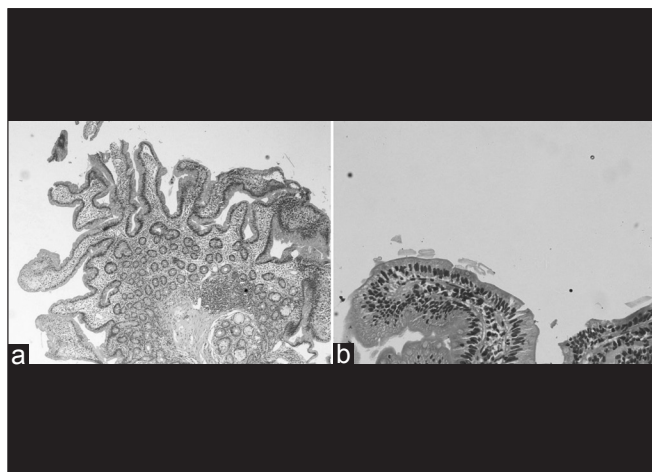


Figure 1: (a) Giemsa stained duodenal biopsy (×4) shows villus to crypt ratio of 3:1, intraepithelial lymphocytes are not increased, no luminal parasite identified, there is mild chronic inflammatory cell infiltrate in the lamina propria features are non specific. (b) Giemsa stained duodenal biopsy (×20) - one villus with same features as described

elevation of TSH and decrease in serum free T₄ caused due to dysfunction of thyroid gland itself. But the same biochemical picture in spite of adequate or excessive supplementation of oral thyroxine might be due to poor compliance of the patient which is the most frequent cause.^[3-5] The other important cause is malabsorption that could be due to GI diseases, pancreatic and liver diseases, dietary interference, or interference due to medications such as antacids, sucralfate, antiepileptics, calcium carbonate amongst others, previous GI surgeries, congestive cardiac failure, and pregnancy.^[6]

In the above case, the patient was very much compliant with oral therapy, and it was also tried under medical supervision and hence poor compliance with the drug was excluded. Defect in the conversion of LT₄ to triiodothyronine (T₃) because of deiodinase-3 deficiency was also suspected which was disproved by her reduced free T₄ levels, unresponsiveness even to oral T₃, and normalization of T₃ also after intravenous T₄ supplementation. Her duodenal biopsy was strikingly normal and not consistent with malabsorptive disease. All other investigations relevant for ruling out intestinal malabsorption were done and all turned out to be normal.

Parenteral levothyroxine (LT₄) is commercially available in 10 ml flip flop single use in 100 µg, 200 µg or 500 µg vials in lyophilized powder form and it is to be stored at 15–30°C. After injection, the synthetic levothyroxine is no way different from endogenous thyroxine. Its distribution, metabolism, and elimination properties are similar to endogenous thyroxine. Replacement or supplemental therapy by intravenous levothyroxine may be done in congenital or acquired hypothyroidism of any etiology when even high doses of oral thyroxine, given for long enough time, fail to achieve euthyroidism and the possibility of deiodinase deficiency and patient noncompliance has been ruled out. Another indication is when rapid repletion of thyroxine is needed, except in cases of transient hypothyroidism. Another important indication is management of myxedema coma using IV levothyroxine.

After enquiry in numerous pharmacies, only one pharmacy could provide the injection levothyroxine at a cost of Rs. 4700 per vial of 200 µg and that was also not routinely available with them. The patient needs to get it by prior intimation. Thus, we see that in our Indian setup the drug is difficult to procure and expensive.

Our patient responded to 10 doses of parenteral T₄, i.e., TSH levels decreased from 370 to 28 µIU/ml and she improved symptomatically. In our Indian setup, where most patients are not covered by insurance, it is highly important

to assess the efficacy of such a costly therapeutic regimen, so we repeated the measurement of TSH after five doses of levothyroxine (15 days) to have an early idea about the response.

To find the cause of this unusual selective malabsorption of oral thyroxine, various ideas can be hypothesized. First is the variation which is observed in the absorption of oral thyroxine.^[7] Second, thyroid hormone is also important for differentiation and growth of intestinal mucosal cells, and hence the altered states of thyroid hormone also might influence the oral hormonal absorption.^[8] The third possible cause could be some specific thyroid hormone uptake defect in the intestinal mucosal cell which can explain the cause for selective malabsorption of thyroid hormone, but this is speculative and not proven so far.

Tönjes *et al.* in 2006 reported a case of refractory hypothyroidism after total thyroidectomy and radioiodine therapy for papillary thyroid cancer, who benefitted by intravenous LT_4 administration five times a week. They also suggested the possibility of a specific intestinal uptake deficit, which became apparent in the case of previous thyroid ablation.^[9] Jauk *et al.* in 2000 reported an unusual case of LT_4 malabsorption in a patient with papillary thyroid cancer after total thyroidectomy and only parenteral therapy led to clinical and biochemical euthyroidism.^[10]

Still the cause of hypothyroidism remains unclear in our patient. But in such cases of refractory hypothyroidism after verifying the compliance with oral therapy and after ruling out all other causes for malabsorption, selective malabsorption of oral thyroxine can be considered and

such patients may be treated with parenteral doses of levothyroxine.

REFERENCES

1. Ain KB, Refetoff S, Fein HG, Weintraub BD. Pseudomalabsorption of levothyroxine. *JAMA* 1991;266:2118-20.
2. Choe W, Hays MT. Absorption of oral thyroxine. *Endocrinologist* 1995;5:222-8.
3. Eledrisi MS, Szymajda A, Alshanti M, Urban RJ. Noncompliance with medical treatment: Pseudomalabsorption of levothyroxine. *South Med J* 2001;94:833-6.
4. Kubota S, Fukata S, Matsuzuka F, Kuma K, Miyauchi A. Successful management of a patient with pseudomalabsorption of levothyroxine. *Int J Psychiatry Med* 2003;33:183-8.
5. Ogawa D, Otsuka F, Mimura U, Ueno A, Hashimoto H, Kishida M, *et al.* Pseudomalabsorption of levothyroxine: A case report. *Endocr J* 2000;47:45-50.
6. Lips DJ, Van Reisen MT, Voigt V, Venekamp W. Diagnosis and treatment of levothyroxine Pseudomalabsorption. *Neth J Med* 2004;62:115.
7. Hays MT. Localization of human thyroxine absorption. *Thyroid* 1991;1:241-8.
8. Hodin RA, Shei A, Morin M, Meng S. Thyroid hormone and the gut. Selective transcriptional activation of a villous enterocyte marker. *Surgery* 1996;120:138-43.
9. Tönjes A, Karger S, Koch CA, Paschke R, Tannapfel A, Stumvoll M, *et al.* Impaired enteral levothyroxine absorption in hypothyroidism refractory to oral therapy after thyroid ablation for papillary thyroid cancer: Case report and kinetic studies. *Thyroid* 2006;16:1047-51.
10. Jauk B, Mikosch P, Gallowitsch HJ, Kresnik E, Molnar M, Gomez I, *et al.* Case history Unusual Malabsorption of Levothyroxine. *Thyroid* 2000;10:93-5.

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