

From Resistance to Relief: IV Levothyroxine in Refractory Hypothyroidism Management

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Abstract:

This case report details the clinical scenario of a 27-year-old female patient diagnosed with idiopathic refractory hypothyroidism. Despite adherence to prescribed oral levothyroxine therapy, she continued to experience persistent symptoms such as fatigue and cold intolerance. The exploration of her condition delved into the complexities of refractory hypothyroidism, encompassing both its diagnostic challenges and therapeutic management. A critical distinction was made between true levothyroxine malabsorption and pseudo-malabsorption, the latter being attributed to issues with medication adherence. The scarcity of research on intravenous levothyroxine use in such cases was noted, highlighting the novelty of this approach. The patient's favorable response to intravenous levothyroxine administration, marked by complete symptom resolution and sustained euthyroid state over four years, provides valuable insights. This case contributes significantly to the existing knowledge on the idiopathic etiologies of refractory hypothyroidism and advocates for the consideration of intravenous levothyroxine as an effective alternative when oral administration proves inadequate.

Key Clinical Message

Patients with idiopathic refractory hypothyroidism who have been identified with oral levothyroxine resistance may benefit from IV levothyroxine as it can alleviate their symptoms and assist physicians in differentiating between true and pseudo-malabsorptive hypothyroidism after excluding any other potential causes.

Introduction:

To restore normal thyroid hormone levels in hypothyroidism, oral levothyroxine sodium (LT4) continues to be the cornerstone of treatment. Levothyroxine absorption can be affected by age, patient compliance, fasting, and the consumption of certain foods or medications (1)(2). Refractory hypothyroidism can have numerous causes, including poor or non-adherence to levothyroxine daily doses, deiodinase deficiency, and various malabsorption disorders. Here we present a case of a 27-year-old female patient with refractory hypothyroidism with no response to oral levothyroxine that was managed with intravenous (IV) levothyroxine.

Differential Diagnosis

Two months later, the patient presented with the same symptoms and required another hospital admission for IV thyroxine due to a suspicion of decreased oral levothyroxine absorption. A duodenal biopsy was taken, which has shown no evidence of *H. pylori*, celiac disease, or any form of dysplasia or malignancy. During that time, the patient had not taken any over-the-counter medications and confirmed compliance with the prescribed medications.

Outcome and Follow-up

Based on the above mentioned findings, and after excluding any other potential cause, the patient was diagnosed with refractory hypothyroidism and was prescribed IV thyroxine 300 mcg three times weekly for the last four years. During the last follow-up visit, the patient was asymptomatic, showing no abnormalities, with a normal range of TSH (**Figure 1**), t_3 , t_4 , and thyroglobulin (**Figure 2**). Additionally, the patient is not complaining of any other medical conditions.

Discussion

Refractory hypothyroidism, a condition where the thyroid gland does not respond adequately to treatment, can arise from a multitude of factors. Non-pathological reasons include patient non-compliance, often due to poor adherence to medication schedules, leading to reduced treatment absorption

. Certain medications, such as proton-pump inhibitors (PPI), histamine receptor blockers, and cholestyramine, along with conditions like irritable bowel syndrome, lactose intolerance, and gastroesophageal reflux disease, can interfere with gastrointestinal absorption. Pregnancy also necessitates specific adjustments in medication dosage across different trimesters. Pathologically, gastrointestinal disorders like inflammatory bowel disease, *H. pylori* infection, and the effects of gastric bypass surgery can contribute to the condition. Furthermore, individual factors such as body mass, gender, and genetic variations specifically in deiodinase

D2 can influence the effectiveness of levothyroxine therapy. It is essential to differentiate true malabsorption from pseudo-malabsorption, which is linked to poor treatment adherence. Idiopathic causes, where the reason remains unknown, account for 10-20% of cases. Understanding these diverse factors is crucial for the effective management of refractory hypothyroidism. (3)(4).

The management of refractory hypothyroidism requires a meticulous and structured approach. Confirming patient adherence to prescribed treatment and proper medication administration techniques is crucial. A thorough review of the patient's medication history is essential to rule out drug interactions that may affect thyroxine levels. Subsequently, conducting tests to investigate potential thyroxine malabsorption is advised, which may include assessing gastrointestinal function and health. For women of childbearing age, a pregnancy test is imperative as pregnancy can alter thyroid hormone levels. Finally, a thyroxine absorption test should be performed to distinguish between pseudo-malabsorption where the issue is not actual malabsorption but perhaps non-compliance or interference, and true levothyroxine (LT4) malabsorption (4).

Treatment in cases of refractory hypothyroidism is achieved by different methods as proposed in different studies of soft gel and liquid LT4 showing potential in specific groups such as pediatric patients, bariatric surgery patients, patients on PPI, and patients unwilling to delay breakfast \RL (5). Parenteral administration is another suggested treatment. This includes subcutaneous (SQ), intramuscular (IM), and intravenous (IV) routes. Hays' mathematical model \RL (6)(7) is used to figure out the doses, and the rates of absorption are twice as high with intramuscular and intravenous administration compared to SQ administration. Moreover, intramuscular administration was reported in multiple cases and favored due to the ability to safely adjust the dose once or twice weekly, which proved to be an acceptable alternative in cases of resistant hypothyroidism to achieve euthymic state in reported patients \RL (7)(8)(9).

Only a limited number of studies in the outpatient setting reported the IV administration of LT4. This was primarily due to its use in hospitalized patients and patients with myxedema. However, given that the IV dose is 75% of the enteral dose and can be administered weekly, it serves as a great substitute for the oral form as evidenced in our study to achieve an euthymic state. This method effectively addresses pseudo-malabsorption and overcomes the factors associated with levothyroxine malabsorption in the GI tract \RL (10)(11)(12)(13)

Conclusion

Idiopathic refractory hypothyroidism is diagnosed by exclusion. The literature has shown various administrative methods for managing such cases. This case exemplifies the difficulties in diagnosing refractory hypothyroidism, particularly the idiopathic form, and it should always be considered in the differential when encountering a patient who is struggling to return to normal status after being prescribed oral levothyroxine, such patients may be treated with parenteral doses of levothyroxine.

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