

## CASE STUDIES

# Combination Therapy in a Hypothyroid Patient Intolerant of Elevated Thyroxine

**Andrea J. Singer, MD**

*Associate Professor of Medicine and Obstetrics and Gynecology  
Georgetown University Medical Center  
Washington, DC*

## INTRODUCTION

Thyroid hormone (TH) replacement therapy has been practiced for more than a century. Nevertheless, the optimal approach to management of hypothyroidism remains controversial. Current treatment guidelines recommend thyroxine ( $T_4$ ) as the preferred therapy for achieving normal thyroid-stimulating hormone (TSH) levels.<sup>1</sup> Although most patients with hypothyroidism are satisfied with  $T_4$  replacement therapy and achieve biochemical euthyroid, some continue to experience symptoms of hypothyroidism.<sup>2</sup> Often, these patients experience debilitating levels of fatigue and may have cognitive disturbances and mood changes, including depression.<sup>2,3</sup> The physiologic basis of patients' symptoms is unclear. Increasing the dose of levothyroxine may be sufficient to establish a clinical euthyroid state, and maintaining patients on treatment—resulting in  $T_4$  levels higher than recommended—is common.<sup>4</sup> Supraphysiologic doses of  $T_4$  frequently cause adverse effects and may result in variable TH levels in peripheral tissues, depending on the background pathology.<sup>5</sup> In this case, a patient whose hypothyroidism was controlled since 1989 with levothyroxine developed symptoms of fatigue and memory loss. The patient was unable to tolerate an increased dose of levothyroxine, but responded well to combination therapy with liothyronine ( $T_3$ ) and levothyroxine.

## CASE DESCRIPTION

### Presentation and History of Present Illness

In 1989, a 50-year-old woman presented with a chief complaint of fatigue and short-term memory problems, and was diagnosed with hypothyroidism, which was treated with levothyroxine. At the time of the patient's second presentation, she was a single parent raising a 5-year-old daughter and had a busy work schedule. She

reported that in previous months she experienced a "low energy level" to varying degrees and felt tired all the time, including on weekends and after sleeping 8 to 10 hours. She also reported poor short-term memory, forgetting what she was doing at the moment, and having trouble focusing on tasks that she previously found easy to complete. Her symptoms were present for several months. Although she was concerned about her symptoms, they had not affected her job performance.

A review of systems revealed no other neurologic complaints. The patient had no history of cardiovascular, respiratory, or renal problems. She described infrequent constipation and joint pain in the right wrist and ankle, as well as occasional dry skin. In addition to the previous diagnosis of hypothyroidism, she had a history of bilateral wrist tendonitis and fibroids. An ovarian cystectomy was performed in 1994, and she reported a previous bilateral arthroscopic knee surgery. She was currently taking 100  $\mu\text{g}/\text{d}$  of levothyroxine, but no other medications. She worked as a lobbyist, was a nonsmoker, and infrequently drank alcohol.

### Physical Examination and Laboratory Studies

The patient was 5 ft, 4 in tall and weighed 138 lbs. She was afebrile, with a pulse rate of 80 bpm, respiration rate of 14 rpm, and blood pressure of 100/60 mm Hg. She had normal reflexes and strength, with normal cerebellar examination and normal Mini-Mental State Examination. Thyromegaly and lymphadenopathy were absent. Her heart had a regular rhythm and S1 and S2 sounds, with no murmurs, rubs, or gallops. Her lungs sounded clear on auscultation and percussion. There was no abdominal tenderness or organomegaly. Skin, hair, and nails looked normal and there was no edema, cyanosis, or clubbing.

A thyroid panel showed a TSH level of 2.1  $\mu\text{IU/L}$  (normal range, 0.5–4.7  $\mu\text{IU/L}$ ), total  $T_3$  of 97 ng/dL (normal, 60–181 ng/dL), and free  $T_4$  of 1.2 ng/dL (normal, 0.8–1.6 ng/dL). Additional laboratory tests revealed that her sodium level was 139 mEq/L, calcium was 9.4 mg/dL, glucose was 94 mg/dL, and hematocrit was 39%.

### Diagnosis and Treatment Strategy

The preliminary diagnosis was *hypothyroidism with fatigue and subjective cognitive and short-term memory impairment*. The patient previously had her dose of levothyroxine increased to 112  $\mu\text{g/d}$ , but the higher dose led to development of palpitations and she complained about a feeling of “jitteriness.” Based on her intolerance of a higher dose of levothyroxine, the decision was made to add a dose of liothyronine to her medication regimen. The patient was started on a regimen of liothyronine 5  $\mu\text{g}$  BID, plus her usual dosage of levothyroxine 100  $\mu\text{g/d}$ .

### Treatment Outcome

On a return visit 6 weeks later, the patient reported feeling better. She said she had no further memory or concentration difficulties and a markedly improved energy level. Laboratory evaluation found a TSH level of 1.81  $\mu\text{IU/L}$ , free  $T_4$  of 1.3 ng/dL, and free  $T_3$  of 0.82 pg/dL (normal range, 0.6–1.81 pg/dL). The patient remained chemically euthyroid on her new regimen of liothyronine 5  $\mu\text{g}$  BID plus levothyroxine 100  $\mu\text{g/d}$ .

### DISCUSSION

The contemporary treatment of hypothyroidism relies on both clinical and laboratory grounds. Often, patients with very high or very low TSH levels are appropriately diagnosed with a thyroid disorder. However, the interpretation of TSH levels within the normal range, in the context of clinical hypothyroidism, continues to challenge clinicians. First, defining a “normal” TSH level remains controversial. More important, although an abnormal TSH level (using the standard definition) is a strong indicator of thyroid dysfunction, a normal TSH does not necessarily indicate the absence of thyroid dysfunction.<sup>6</sup>

Transformation of administered  $T_4$  to  $T_3$  does not always mimic the physiologic state, as shown by evi-

dence from animal studies, clinical trials, and patient preferences.<sup>7</sup> The addition of  $T_3$  to  $T_4$  therapy remains experimental, and questions remain as to which patients are the best candidates, and what  $T_4$ -to- $T_3$  ratio is ideal for therapy.<sup>3</sup> Unfortunately, serum  $T_3$  levels do not seem to be helpful in identifying patients who could potentially benefit from combination therapy.

For this patient, a previous adverse response to a relatively low levothyroxine dosage provided a strong rationale for adding liothyronine to her regimen. Because low doses of levothyroxine and liothyronine were sufficient to attain clinical and chemical euthyroidism, such a regimen is not likely to be associated with a risk of adverse events. Nevertheless, any patient treated with THs should be monitored regularly to prevent overtreatment and the associated risk of cardiac arrhythmias and osteoporosis.<sup>8</sup>

### REFERENCES

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