Polyneuropathy after Radioactive Iodine Treatment of Hyperthyroidism and Beneficial Effect of Combined T4/T3 Therapy of Hypothyroidism

Stasa Ivkovic

Clinical Center of Serbia, Clinic of Otorhinolaryngology and Maxillofacial Surgery, Belgrade, Serbia

Dear Sir,

Five months after radioactive iodine treatment for Graves' hyperthyroidism, I developed severe hypothyroidism. Three months after treatment, TSH, FT4 and FT3 values were within reference range (0.44 mIU/l, 15.9 and 4.5 pmol/l, respectively), but 7 weeks later, FT4 level was 2.6 pmol/l, and the highest level of TSH was 75

mIU/l. The symptoms of sensitive polyneuropathy manifested soon after introducing levothyroxine therapy. Fatigue, lack of concentration, forgetfulness, depression, and widespread neuropathic pain persisted more than 2 years in spite of levothyroxine replacement therapy (125 µg levothyroxine daily) and TSH level of

about 1 mIU/l. The levels of total and LDL cholesterol were increased. ENG showed sensitive, predominantly axonal polyneuropathy of the smaller nerves in the lower extremities and arms (table 1). Extensive clinical investigation did not find any potential cause of polyneuropathy other than hypothyroidism.

Table 1. Nerve conduction examination

Nerves	MTL ms	MCV ms	MA mV	SCV m/s	SNAP amp. µV	F wave ms
Median	2.8	56.4	10.2	61.9	14	24.8
Reference values	2.78 ± 0.41	58.78 ± 4.41	14.62 ± 8.45	60.88 ± 5.07	30.93 ± 12.07	<30.142
Ulnar				63.8	26	
Reference values				60.93 ± 5.17	22.74 ± 14.43	
Peroneal right	4.2	53.8	1.0			–
Reference values	3.72 ± 0.53	49.51 ± 3.93	10.09 ± 4.81			
Peroneal left	4.8	53.7	3.0			50.6
Reference values	3.72 ± 0.53	49.51 ± 3.93	10.09 ± 4.81			<52.292
Sural				45.5	2.9	
Reference values				54.48 ± 5.16	18.02 ± 8.27	
Medial antebrachial cutaneous				67.7	2.6	
Reference values				49.3 ± 3.8	10–30	
Peroneal superficial				51.9	2.3	
Reference values				65.7 ± 3.7	20.5 ± 6.1	
Radial				52.6	11	
Reference values				56.7 ± 5.0	34.3 ± 14.2	

MTL = Motor terminal latency; MCV = motor conduction velocity; MA = motor amplitude; SCV = sensory conduction velocity; SNAP amp. = sensory nerve action potential amplitude.

Then I introduced combined T4/T3 therapy on my own, i.e., 100 µg of T4 and 10 µg of T3 administered in 2 daily doses. Positive effects on cognition and mood appeared very fast and were very impressive. During levothyroxine treatment, my FT3/FT4 concentration ratio in serum was low (table 2). During T4/T3 treatment, this ratio was physiological 2 h after taking the medicine (table 3) [1]. During levothyroxine treatment 125 µg/day, the serum FT4 concentration was slightly above reference range, while TSH concentration was within limits 2 h after receiving the medicine – which was the proof of a reduced sensitivity of the thyroid-pituitary feedback mechanism, reflecting the inadequacy of peripheral deiodination to compensate for the absent T3 secretion (table 2) [1]. Total cholesterol serum concentration dropped significantly after the introduction of combined T4/T3 therapy. The same applied to LDL cholesterol (table 3).

TSH serum concentrations were approximately the same with LT4 and combined T4/T3 therapy, 0.57 and 0.70 mIU/l, respectively (table 2, 3).

During levothyroxine monotherapy, my hands were cold, especially in winter. It was unusual for me. This winter, being treated with T4/T3 therapy, my hands have become warm. This could be the consequence of a stronger effect of combined T4/T3 therapy on normalization of the peripheral vascular resistance [2].

Five months after starting the combined T4/T3 therapy, I still have the symptoms of sensitive polyneuropathy. Nevertheless, the symptoms are not so severe and do not interfere with my sleep. Endocrinologists whom I have visited are not familiar with the association between hypothyroidism and sensitive polyneuropathy. But, there is an extensive scientific literature addressing this topic. Sensitive polyneuropathy is common in untreated or treated clinical or even subclinical hypothyroidism, independently of the cause of the disease [3, 4, 6–9]. On the other hand, T3 is the most powerful neurotrophic substance in nature [5]. There is a huge difference among athyroid patients in T3 production capacity from orally administered levothyroxine [1]. Therefore, suboptimal intraneuronal T3 concentration in levothyroxine therapy due to polymorphic variation in thyroid pathway genes could be the reason for persisting peripheral nerve damage or development of polyneuropathy years after starting levothyroxine

Table 2. Serum free thyroid hormone and TSH, FT3/FT4 ratio, cholesterol, LDL, HDL, and triglycerides levels while being treated with LT4 therapy

Variables	Measured values		Reference values
	1st time point	2nd time point	
FT4, pmol/l	22.80	16.14	12.0–22.0
FT3, pmol/l	4.21	4.15	3.10–6.80
TSH, mIU/l	0.57	1.70	0.27–4.20
FT3/FT4	0.18	0.26	
Cholesterol, mmol/l	6.30	5.90	0–5.20
LDL, mmol/l	4.20	4.05	0–3.40
HDL, mmol/l	1.68	1.47	≥1.0
Triglycerides, mmol/l	0.92	0.82	0–1.70

Serum samples obtained 2 h after the ingestion of 125 µg levothyroxine (1st time point) and 100 µg levothyroxine (2nd time point).

Table 3. Serum free thyroid hormone and TSH, FT3/FT4 ratio, cholesterol, LDL, HDL, and triglycerides levels while being treated with combined T4/T3 therapy (levothyroxine 100 µg, triiodothyronine 10 µg) administered in 2 daily doses

Variables	Measured values		Reference values
	1st time point	2nd time point	
FT4, pmol/l	15.60	15.80	12.0–22.0
FT3, pmol/l	5.17	5.68	3.10–6.80
TSH, mIU/l	0.70	1.12	0.27–4.20
FT3/FT4	0.33	0.36	
Cholesterol, mmol/l	5.38	5.44	0–5.20
LDL, mmol/l	3.60	3.50	0–3.40
HDL, mmol/l	1.41	1.48	≥1.0
Triglycerides, mmol/l	0.76	0.96	0–1.70

Serum samples obtained 2 h after the ingestion of T4 50 µg and T3 5 µg (1st time point) and 3 h after the ingestion on separate occasions (2nd time point).

therapy in some patients [1, 5, 10–14]. Time and control ENG will tell if definite beneficial effects of combined T4/T3 therapy on peripheral nerves will be achieved in my case. I have not observed any undesirable effect of combined T4/T3 therapy during the first 5 months of treatment.

I have to state that widely accepted levothyroxine monotherapy and its reputation of a simple and effective therapy for hypothyroidism neglects the fact that a significant number of patients treated with this therapy have lifelong hypothyroid symptoms which make them less pro-

ductive or even unproductive members of society. A great ethical issue is the fact that some patients with hypothyroidism, resulting from the radioactive iodine or surgical treatment of hyperthyroidism, have symptoms of hypothyroidism in spite of levothyroxine therapy, but they have not been advised about it before treatment.

Disclosure Statement

I do not have any conflict of interest.

References

- 1 Gullo D, Latina A, Frasca F, Le Moli R, Pellegriti G, Vigneri R: Levothyroxine monotherapy cannot guarantee euthyroidism in all athyreotic patients. *PLoS One* 2011; 6:e22552.
- 2 Dickman MJM, Harms MPM, Endert E, Wieling W, Wiersinga WM: Endocrine factors related to changes in total peripheral vascular resistance after treatment of thyrotoxic and hypothyroid patients. *Eur J Endocrinol* 2001;144:339–346.
- 3 Beghi E, Delodovici M, Bogliun G, Crespi V, Paleari F, Gamba P, Capra M, Zarrelli M: Hypothyroidism and polyneuropathy. *J Neurol Neurosurg Psychiatry* 1989;52:1420–1423.
- 4 Nebuchennykh M, Loseth S, Mellgren SI: Aspects of peripheral nerve involvement in patients with treated hypothyroidism. *Eur J Neurol* 2010;17:67–72.
- 5 Barakat-Walter I: Role of thyroid hormones and their receptors in peripheral nerve regeneration. *J Neurobiol* 1999;40:541–559.
- 6 Penza P, Lombardi R, Camozzi F, Ciano C, Lauria G: Painful neuropathy in subclinical hypothyroidism: clinical and neuropathological recovery after hormone replacement therapy. *Neurol Sci* 2009;30:149–151.
- 7 Magri F, Buenocore M, Oliveira A, Rotondi M, Gatti A, Accornero S, Camera A, Chiovato L: Intraepidermal nerve fiber density reduction as a marker of preclinical asymptomatic small fiber sensory neuropathy in hypothyroid patients. *Eur J Endocrinol* 2010; 162:279–284.
- 8 Dick DJ, Lane RJM, Nogues MA, Fawcett PRW: Polyneuropathy in occult hypothyroidism. *Postgrad Med J* 1983;59:518–519.
- 9 Monzani F, Caraccio N, Del Guerra P, Casolaro A, Ferrannini E: Neuromuscular symptoms and dysfunction in subclinical hypothyroid patients: beneficial effect of LT4 replacement therapy. *Clin Endocrinol* 1999; 51:237–242.
- 10 Bauer M, Heinz A, Whybrow PC: Thyroid hormones, serotonin and mood: of synergy and significance in the adult brain. *Mol Psychiatry* 2002;7:140–156.
- 11 Panicker V, Saravanan P, Vaidya B, Evans J, Hattersley AT, Frayling TM, Dayan CM: Common variation in the DIO2 gene predicts baseline psychological well-being and response to combination thyroxine plus triiodothyronine therapy in hypothyroid patients. *J Clin Endocrinol Metab* 2009;94: 1623–1629.
- 12 Wiersinga WM: Do we need still more trials on T4 and T3 combination therapy in hypothyroidism? *Eur J Endocrinol* 2009;161:955–959.
- 13 Samollow PB, Perez G, Kammerer CM, Finegold D, Zwartjes PW, Havill LM, Comuzzie AG, Mahaney MC, Goring HH, Blanegro J, Foley TP, Barmada MM: Genetic and environmental influences on thyroid hormone variation in Mexican Americans. *J Clin Endocrinol Metab* 2004;89:3276–3284.
- 14 Gereben B, Yavacki AM, Ribich S, Kim BW, Huang SA, Simonides WS, Zeold A, Bianco AC: Cellular and molecular basis of deiodinase-regulated thyroid hormone signaling. *Endocr Rev* 2008;29:898–938.