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THE ACUTE MYXEDEMA AFTER HYPERTHYROIDISM TREATED BY RADIOACTIVE IODINE AND ITS SEQUELAE

This is a case report of a female patient who developed, after radioactive iodine therapy for Grave's hyperthyroidism, a severe clinically manifested hypothyroidism, which was accompanied by predominantly sensory neuropathy of dominant axonal type. Besides symptoms and neurophysiological signs of polyneuropathy, the patient, in spite of seemingly adequate levothyroxine monotherapy for hypothyroidism during the last 2 years, still manifested persistent hypothyroid symptoms by CNS, higher serum concentrations of total and LDL cholesterol and clinical signs of the increased peripheral vascular resistance. Non-physiological serum FT3 and FT4 ratio was maintained, together with serum TSH and FT4 concentrations, which suggested lower sensitivity of thyroid-hypophyseal negative feedback.

The introduced combined LT4/LT3 substitution therapy resulted in quick subsidence of CNS-related hypothyroid symptoms, significant reduction of serum concentrations of total and LDL cholesterol, FT3/FT4 ratio normalization, at least in the first hours of drug administration, and disappearance of clinical signs of the increased peripheral vascular resistance. The extent of polyneuropathic difficulties was reduced to the level of not disturbing the sleep. Time and control ENG will show the final effects of combined T4/FT3 therapy on the peripheral nerve injuries. In the first 6 months, no adverse effects of this therapy were recorded.

Key words: radioactive iodine, hypertyroidism, polyneuropathy, hypothyroidism, T4/T3 therapy

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Introduction

Radioactive iodine therapy is considered very reliable and safe treatment in case of definitive management of autoimmune hyperthyroidism – Grave's disease. It is often used in the USA as the initial therapy of this disease. Expert literature reports that the only possible complication is a development of permanent hypothyroidism; therefore, many authors believe that an early onset of hypothyroidism is desired objective of therapy, given that, from long-term aspect, it is impossible to avoid such outcome; yet, hypothyroidism is allegedly very easy to treat (1).

Case Report

This is a case report of 41-old female patient treated by radioactive iodine for Grave's disease. The patient was diagnosed with hyperthyroidism in her 28 years of age. She was medicamentously treated with propylthiouracil for a long time. Remission ensued after 6 years of treatment. Three years later, the disease recurred. In the following 3 years, the same therapy was repeated, followed by radioactive iodine in a dose of 11mCi. Three months later, the patient was in euthyroid state. She was extremely well and symptom-free. The next control was scheduled in 3 months. Nevertheless, some ten days later, the patient manifested exacerbation of the chronic sinusitis and was treated several weeks without any success. This period was featured by fatigue, asthenia, indisposition and hoarseness. Seven weeks after the previous control visit, she had sudden deterioration of her general health condition, reflecting in fatigue and tachycardia. Laboratory test results indicated severe hypothyroidism: TSH - 60 ml U/l, and FT4 2.6 pmol/l (Table1). Soon after the onset of levothyroxine substitution therapy, neurological symptoms were developed. Sudden symmetrical hand paresthesia made patient waking from her sleep. At the same time, continuous sensation of straining and burning of the anterior abdominal wall was present. In addition, severe symptoms of hypothyroidism of all organ systems were manifested in the following two months as well as often attacks of feeling of suffocation and tachycardia, sleep apnea syndrome, panic attacks for several times, hoarseness, asthenia, depression, vertigo, discrete dysarthria, and difficulty with swallowing. ECG showed remarkably low-voltage, diffuse flattening and biphasic T waves with slightly widened QRS complex (Figure 1). Echocardiographic finding was normal. Laboratory analyses showed higher CK and serum cholesterol values.

After reaching the laboratory euthyroid state, paresthesias became generalized and permanent, and gradually gained the quality of neuropathic pains. Neurological findings were regular. The initial ENG failed to verify the signs of polyneuropathy. Serum and urine protein electrophoresis was normal. Serum and urine protein immunofixation was also normal. HBs Ag and anti HCV antibodies were negative.

Immunological analyses showed the presence of p-ANCA antibodies in titre with the initial finding of 1:80, and then 1:20, and finally negative, and anti MPO antibodies were slightly increased -7,7 U/ml (upper limit to 5U/ml). ANA antibodies were negative, and only once anti Ro SSA antibodies were found mildly higher - 56 U/ml(normal to 25U/ml), but several months later, the results were normal – 5 U/ml. Antiparietal, antigliadin and endomysial antibodies were negative. Cryoglobulins were negative. Serum immunoglobulins were normal. Immune complexes were not present. Glucose stress test was normal (Table 2).

Upon neurological evaluation, thyroid small fiber polyneuropathy was presumed and symptomatic Lyrica and Amitriptyline oral therapy was recommended, but due to adverse effects and inadequate efficacy, the therapy was discontinued after 4 weeks.

Two years after radioactive iodine therapy, the ENG findings suggested to more sensory, dominant axonal neuropathy of smaller fibers in the upper and lower extremities (Table 3).

In spite of substitutional levothyroxine 125 mcg/day therapy and serum TSH concentration of about 1 mlU/l, her asthenia, lower concentration, obliviousness, depression and generalized neuropathic pains persisted. Ratio of serum FT3/FT4 concentrations was decreased. In addition, higher serum total and LDL cholesterol levels were also persistent.

An expert opinion of thyreodologist was that polyneuropathy could not be associated with either hypothyreosis or therapeutical procedures, and that polyneuropathy should be treated exclusively by neurologist; and, her depressive symptoms ought to be managed by psychiatrist.

Two-and-a half years after the onset of hypothyroidism, combined L thyroxin 100mcg and L triiodothyronine 10mcg therapy was introduced, divided in 2 daily doses. Very soon, CNS-related hypothyroid symptoms subsided. The extent of polyneuropathic difficulties, during the first six months of combined therapy, was very gradually decreased to the level not disturbing the sleep. Moreover, the patient noted that her hands were again warm, in distinction from former two winters when she was covered by L thyroxin monotherapy. Serum FT3/FT4 ratio was also restored to normal, at least within the first hours of drug administration (Table 5). Serum TSH levels were almost the same in monotherapy L thyroxin 125mcg/day and combined T4/T3 therapy (Tables 4 & 5).

Discussion

The association between polyneuropathy and hypothyroidism is not widely known among endocrinologists. There is even the internet site where these patients exchange their experience, complaining of the same problem that their endocrinologists fail to

see the connection between hypothyroidism and polyneuropathy (1). Nevertheless, one may find an extensive literature addressing this issue. Sensory polyneuropathy appear in both untreated and treated clinical, even subclinical hypothyroidism, regardless of the cause of hypothyroidism. (3),(4),(6),(7),(8),(9),(10),(11)

Ettore Beghi and assoc. found that 64% of 39 patients with primary hypothyroidism of different causes, duration and not depending upon the beginning of treatment, had subjective polyneuropathic difficulties, and electroneurographic diagnosis of polyneuropathy was established in 72% of cases (3).

Flavia Magri and assoc. found lowered density of intraepidermal nerve fibers in 60% of patients with the untreated clinical hypothyroidism and in 25% with the untreated subclinical hypothyroidism (4), and they documented the increase of intraepidermal nerve fibers density in these patients after L thyroxin therapy (5).

Kristin Orstavik and assoc. concluded that some patients with treated hypothyroidism had the symptoms of small fibre neuropathy (6).

Penza P and assoc. described the case of a female patient whose symptoms of small fibre polyneuropathy were the first signs of subclinical hypothyroidism. Substitution levothyroxine therapy resulted in complete clinical and neuropathological recovery (7).

Fabio Monzani and assoc. established high frequency of neuromuscular symptoms in patients with subclinical hypothyroidism and recovery following the introduction of substitution levothyroxine therapy (8).

D.J.Dick and assoc. described a patient with the sensory neuropathy as the only symptom of severe hypothyroidism. Substitution L thyroxin therapy led to complete clinical and ENG recovery (9).

Accordingly, sensory neuropathy may be caused by hypothyroidism. It is given little thought to because it is very often mild, and patients even miss to mention the symptoms, and it is also often subclinical (4). In some patients, subjective symptoms and objective signs (pathological ENG finding and reduced density of peripheral nerve endings on the skin) subside after L thyroxin therapy, and in some they tend to be persistent (3),(5) (6),(7),(8),(9), (10),(11). Some patients have the first polyneuropathic disorders only few years after the beginning of substitution levothyroxine therapy (3), independently from whether the cause of hypothyreosis is an autoimmune thyroid disease or not (3). The association of sensory polyneuropathy and subclinical hypothyroidism points to the fact that even very subtle deficit of thyroid hormones may cause damage of peripheral nerves (4),(7),(8). Pathogenetic mechanism of peripheral nerve damage in hypothyroidism has not been fully clarified. Diminished mitochondrial availability of high-energy phosphates for oxidative metabolism, along with lower activity of Na+/K+ pump and change of activity-dependent axonal transport are probable causes of axonal damage in hypothyroidism (11). Reduced blood flow in vasa nervorum due to edema and increased peripheral vascular resistance is a probable contributing factor.

The fact that the first symptoms of polyneuropathy appeared in our patient not before the onset of substitution levothyroxine therapy suggested to possible analogy with the reperfusion lesions to the myocardium after successful reperfusion therapy in the acute myocardial infarction, and with the development of polyneuropathy in diabetics after the abrupt diabetes regulation by high insulin doses.

In our patient, the initial symptom of hypothyroidism was exacerbation of chronic sinusitis due to edema of paranasal sinus ostium caused by imminent hypothyroidism. Because of rapid worsening of hypothyroidism, therapy for sinusitis was ineffective, and the patient ascribed her fatigue, asthenia and apathy to persistent sinusitis. This is the fact which gives a warning that hypothyroidism is an extremely insidious disease, even if it appears abruptly and is actually expected. In addition, you can never predict the first symptom in the respective patient.

During the L thyroxin monotherapy, non-physiological serum FT3 and FT4 ratio was maintained (Table 4). In euthyroid people with healthy thyroid gland, mean FT3/FT4 ratio is 0.32(12). In our patient during monotherapy with L thyroxin 125 mcg/day, this ratio was 0.18 (Table 4). Upon introduction of T4/T3 therapy, this ratio was 0.33 two hours after the drug administration, corresponding to physiological ratio (Table 5). During L thyroxin 125 mcg/day therapy, serum FT4 was slightly above the upper reference limit, while serum TSH concentration was within the limits 2 hours after drug ingestion, indicating reduced sensitivity of thyroid-hypophyseal negative feedback as a consequence of inability of peripheral deiodination to compensate for lack of thyroid T3 secretion (12) (Table 4). Total and LDL cholesterol values during L thyroxin monotherapy were increased. (Table 4). During combined LT4/LT3 therapy, a significant fall of serum total and LDL cholesterol concentrations were present (Table 5). L thyroxin monotherapy, regardless of the applied dose, failed to restore serum total and LDL cholesterol values to the level before hypothyroidism or time when the patient was in euthyroid state on thyroid suppressive therapy or before that in remission. Combined LT4/LT3 therapy enabled to maintain these concentrations just on that level. It was an indirect confirmation that L thyroxin monotherapy, regardless of the applied dose, was not sufficient to provide as much active thyroid hormone, triiodothyronine, as required for cholesterol metabolism to be as it was before the onset of hypothyroidism , when thyroid hormones originated from functional thyroid gland. After the beginning of combined LT4/LT3 therapy, the patient noticed that her hands were again warm. It could be the consequence of stronger effect of combined T4/T3 therapy to normalization of peripheral vascular resistance, because serum FT3 concentration is the only thyroid function parameter which is indirectly associated with the peripheral vascular resistance value in hyperthyroid patients covered by thyroid suppression therapy and in hypothyroid patients on substitution L thyroxine therapy (13). Serum TSH concentrations were approximately the same during LT4 and combined LT4/LT3 therapy (Tables 4 and 5).

Thyroid hormones have major role in maintaining the normal function and integrity of the central and peripheral nervous system. It has a significant role in the regulation of the central noradrenergic neurotransmission as well as function of serotonergic and dopaminergic systems. Thyroid hormones may be found in high concentrations in the cortical tissue, opposite to peripheral tissues where T4 concentrations far exceed T3 concentration, namely T4 and T3 are in equimolar ratio in the brain. It accordingly follows that adequate intraneuronal concentrations of biologically most potent thyroid hormone, triiodothyronine, have an extreme significance for brain functioning (14).

Numerous experimental studies have shown the significance of T3 in regeneration of injured peripheral nerves, and therefore, its application in the respective therapy has been considered (15),(16),(17),(18). Triiodothyronine has larger effect on regeneration of peripheral nerves than any growth factor or adhesion molecule. It is the most potent neurotrophic substance in nature. It is the result of its multiple effects on gene expression of a number of growth factors, intercellular matrix and cell adhesion molecules (19).

The most probable cause of polyneuropathy in our patient was the acute iatrogenic myxedema due to ill-timed introduction of substitution therapy with thyroid hormones, what was the consequence of high dose and too large interim period between recommended controls after the application of therapeutical radioactive iodine doses. There are major interindividual differences in the capacity of serum T4 and T3 conversion among athyroid patients on L thyroxin monotherapy, and on the average, they have far lower serum FT3 concentrations in relation to individuals with healthy thyroid gland (12). Population studies have shown that serum FT3 concentration is a parameter with the highest interindividual variability of all laboratory parameters of thyroid function (20). Triiodothyronine has a distinctive circadian rhythm, which follows TSH circadian rhythm with certain time delay, suggesting its thyroidal origin and great physiological significance (21). During L thyroxin monotherapy in our patient, the symptoms of polyneuropathy and hypothyroid symptoms related to CNS maintained simultaneously. During combined T4/T3 therapy, the aforementioned symptoms almost completely disappeared, and polyneuropathic problems were significantly reduced. It is possible that L thyroxin monotherapy in our patient could not ensure enough serum FT3 concentration to reach optimal intraneuronal T3 concentration necessary for maintaining the normal function and structural integrity of the central and peripheral nervous system according to specific thyroid phenotype. Genetic polymorphism at the level of D2 deiodinase and thyroid transporters could also modify triiodothyronine availability in nerve cells (22).

One should also consider the probable role of autoimmunity in pathogenesis of polyneuropathy. It is possible that our patient had low titre positive p-ANCA antibodies even earlier because of long-term therapy with Propylthiouracil (23). Anti TPO

antibodies were moderately and then slightly increased after radioactive iodine therapy. Probably, these were the sequelae of autoimmunization during the disintegration of thyreocytes after radioactive iodine therapy.

Study results indirectly suggest to metabolic nature of hyperthyroid neuropathy, and so far, there has not been any scientific evidence for the autoimmune-related nature of hypothyroid neuropathy (3). Moreover, the initial symptoms of polyneuropathy appeared in our patient when she was in the condition of most severe, sudden and clinically manifested hypothyroidism, concurrently with many other hypothyroid symptoms.

Conclusion

The presented case report suggests that radioactive iodine therapy for hyperthyroidism may cause damage of peripheral nerves. The most probable cause of such injury is a development of the acute myxedema due to ill-timed introduction of substitution therapy with thyroid hormones; persistence of these lesions during substitution levothyroxine therapy could be a sign of inadequacy of such therapy or irreversibility of damage of the peripheral nerves because of severity of hypothyroid condition and its rapid occurrence. One should also consider a possibility of the role of thyroid autoimmunity in pathogenesis of polyneuropathy and low probability of direct toxic effect of radioactive iodine. After the application of therapeutical radioactive iodine doses, the controls for thyroid hormone levels are far more frequently required than recommended in clinical practice (2), (24), and the doctors must be aware of the risk of unrecognized dysfunction of thyroid gland and consequential brutal metabolic collapse (25)(26).

In our patient, combined T4/T3 therapy had favorable effects on hypothyroid symptoms related to the central nervous system; it led to significant reduction of serum total and LDL cholesterol levels and normalization of serum FT3 and FT4 concentration ratio, at least in the first hours after drug administration. In addition, the clinical signs of decrease, that is, normalization of peripheral vascular resistance (warm hands) were manifested, too. Further clinical and ENG monitoring will show the long-term effect of this therapy on hypothyroid sensory polyneuropathy. No side effects were recorded in the first six months of combined T4/T3 therapy.

The case of our patient illustrates in multiple ways the complexity of functional impairments of thyroid gland, and an extraordinary complexity of therapeutical approach, which has been, unfortunately, simplified too often in clinical practice (2). Clinical and laboratory parameters during L thyroxin monotherapy for hypothyroidism and the change of these parameters during combined LT4/LT3 therapy clearly point to presence of continuous deficit of triiodothyronine during LT4 monotherapy in our patient. Considering a huge significance of an optimal intracellular triiodothyronine

concentration for many tissues and organs, and primarily for nervous and cardiovascular systems, the chronic triiodothyronine deficiency may unfavorably reflect on both the quality of life and morbidity, before all cardiovascular and cerebrovascular one, and consequently to mortality rate as well (14)(27). Higher cardiovascular and cerebrovascular mortality rates reported by some studies in patients treated by radioactive iodine for hyperthyroidism could be caused by disadvantages of substitution levothyroxine therapy in these patients rather than by some ancient hyperthyroid state as believed by some authors (2),(28),(29)(30).

A special ethical issue facing the endocrinology community is the fact that a considerable number of patients (10-15%) with hypothyroidism, after their therapy with radioactive iodine or surgery, have long-life hypothyroid symptoms in spite of substitution levothyroxine therapy, and that they have not been informed on such problem on time. (30)

Given the contemporary knowledge on large interindividual genetic differences at all levels of complex and insufficiently studied thyroid system, it is necessary to exercise an individual approach to patient in the management of functional disorders of thyroid gland (20), (22), (31).

Figure 1. ECG on the beginning of substitutional L thyroxine therapy

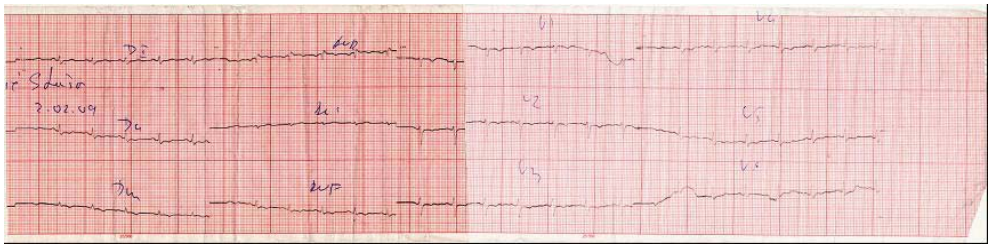

Table 1. Laboratory analyses during hypothyroidism

Analysis	Values	Reference values
FT4, pmol/l	2,6	9,1 – 23,9
TSH, mlU/l	75	0,27 – 4,2
CK, U/l	409	< 150
LDH, U/l	529	220 – 460
Cholesterol, mmol/l	8,36	<5,2
LDL, mmol/l	5,9	<3,4
HDL, mmol/l	1,46	> 1,6
Triglycerides, mmol/	12,15	<1,7

Table 2. Laboratory analyses during examination of polyneuropathy

Analysis	Measurement 1	Measurement 2	Reference values
Serum protein electrophoresis	Regular		
Urine protein electrophoresis	Regular		
Serum protein immunofixation	Regular		
Serum protein immunofixation	Regular		
HBsAg, anti HCV	Negative		
ANA	Negative		
p-ANCA	1:80	1:20	
Anti-MPO	9.2	7.7	<5U/ml
AntiRo SSA 52/60	56.6	5.0	<25U/ml
Antiparietal At	Negative		
Endomysial At	Negative		
Antigliadin At	Negative		
Cryoglobulins	Negative		

Table 3. Electroneurographic findings

	Terminal latency (ms)	Motor velocity (ms)	Motor EP amplitudes (mV)	Sensory conduction velocity (m/s)	Sensory EP amplitudes (uV)	F wave latency (ms)
n. medianus	2.8 (2.78+-0.41)	56.4 (58.78+-4.41)	10.2 (14.62+-8.45)	61.9 (60.88+-5.07) 63.8 (60.93+-5.17)	14 (30.93+- 12.07) 26 (22.74+-14.43)	24.8 (<30.142)
n. ulnaris						-
n. peroneus dexter	4.2 (3.72+-0.53)	53.8 (49.51+-3.93) 53.7	1.0 (10.09+-4.81) 3.0			50,6 (< 52.292)
n. peroneus sinister	4.8			45.5 (54.48+-5.16)	2.9 (18.02+-8.27)	
n. suralis				67.7 (49.3+-3.8) 51.9 (65.7+-3.7) 52.6 (56.7+-5.0)	2.6 (10-30) 2.3 (20.5+-6.1)	
n. cutaneus antebrachii medialis					11 (34.3+-14.2)	
n. peroneus superficialis						
n. radialis						

Tabela 4. Serumske koncentracije tireoidnih hormona i lipida tokom LT4 terapije

	Measured values		Reference values	
	1. measurement	2. measurement		
FT4	22.8	16.14	12-22	pmol/l
FT3	4.21	4.15	3.1-6.8	pmol/l
TSH	0.57	1.70	0.27-4.2	mlU/L
FT3/FT4	0.18	0.26		
Cholesterol	6.3	5.9	0-5.2	mmol/l
LDL	4.2	4.05	0-3.4	mmol/l
HDL	1.68	1.47	>=1	mmol/l
Triglycerides	0.92	0.82	0-1.7	mmol/l

Serum samples collected 2h after oral dose of L thyroxine 125 mcg (1. measurement) and L thyroxine 100 mcg (2. measurement)

Table 5. Serum concentrations of thyroid hormones and lipids during combined T4/T3 therapy (L thyroxin 100 mcg, triiodothyronine 10 mcg) divided in 2 daily doses

	Izmerene vrednosti		Ref. vrednosti	
	1. merenje	2. merenje		
FT4	15.6	15.8	12-22	pmol/l
FT3	5.17	5.68	3.1-6.8	pmol/l
TSH	0.7	1.12	0.27-4.2	mlU/L
FT3/FT4	0.33	0.36		
Cholesterol	5.38	5.44	0-5.2	mmol/l
LDL	3.6	3.5	0-3.4	mmol/l
HDL	1.41	1.48	>=1	mmol/l
Triglycerides	0.76	0.96	0-1.7	mmol/l

Serum samples collected 2 h after oral dose of LT4 50 mcg and LT3 5 mcg (1. measurement) and after 3h (2. measurement)

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