

# Chronic severe axonal polyneuropathy associated with hyperthyroidism and multivitamin deficiency

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## Abstract

**OBJECTIVES:** Hyperthyroidism is often associated with various neuromuscular disorders, most commonly proximal myopathy. Peripheral nerve involvement in hyperthyroidism is very uncommon and has rarely been reported. We describe a 29-year-old woman with untreated hyperthyroidism who presented with chronic severe axonal sensory-motor polyneuropathy. Peripheral nerve involvement developed together with other symptoms of hyperthyroidism 2 years before presentation. She also had anorexia nervosa for the past 6 months, resulting in multivitamin deficiency.

**RESULTS:** Electrophysiological and pathological findings as well as clinical manifestations confirmed the diagnosis of severe axonal polyneuropathy. Anorexia nervosa has been considered a manifestation of untreated hyperthyroidism. We considered hyperthyroidism to be an important causal factor in the polyneuropathy in our patient, although peripheral nerve involvement in hyperthyroidism is rare. To our knowledge, this is the first documented case of chronic severe axonal polyneuropathy ascribed to both hyperthyroidism and multivitamin deficiency.

**CONCLUSION:** Our findings strongly suggest that not only multivitamin deficiency, but also hyperthyroidism can cause axonal polyneuropathy, thus expanding the clinical spectrum of hyperthyroidism.

## INTRODUCTION

Hyperthyroidism is often associated with various neuromuscular disorders, most commonly proximal myopathy and myasthenia gravis. Peripheral nerve involvement in hyperthyroidism is very uncommon and has rarely been reported (Swanson *et al.* 1981; Duyff *et al.* 2000; Marino *et al.* 1997). A recent study reported that a few patients with

untreated hyperthyroidism had electrophysiologic evidence of mild axonal degeneration (Duyff *et al.* 2000), but pathologically confirmed axonal degeneration has not been reported previously.

We describe a 29-year-old woman with untreated hyperthyroidism who presented with chronic severe axonal sensory-motor polyneuropathy. She also had anorexia nervosa for the past 6 months, resulting in multivitamin deficiency.

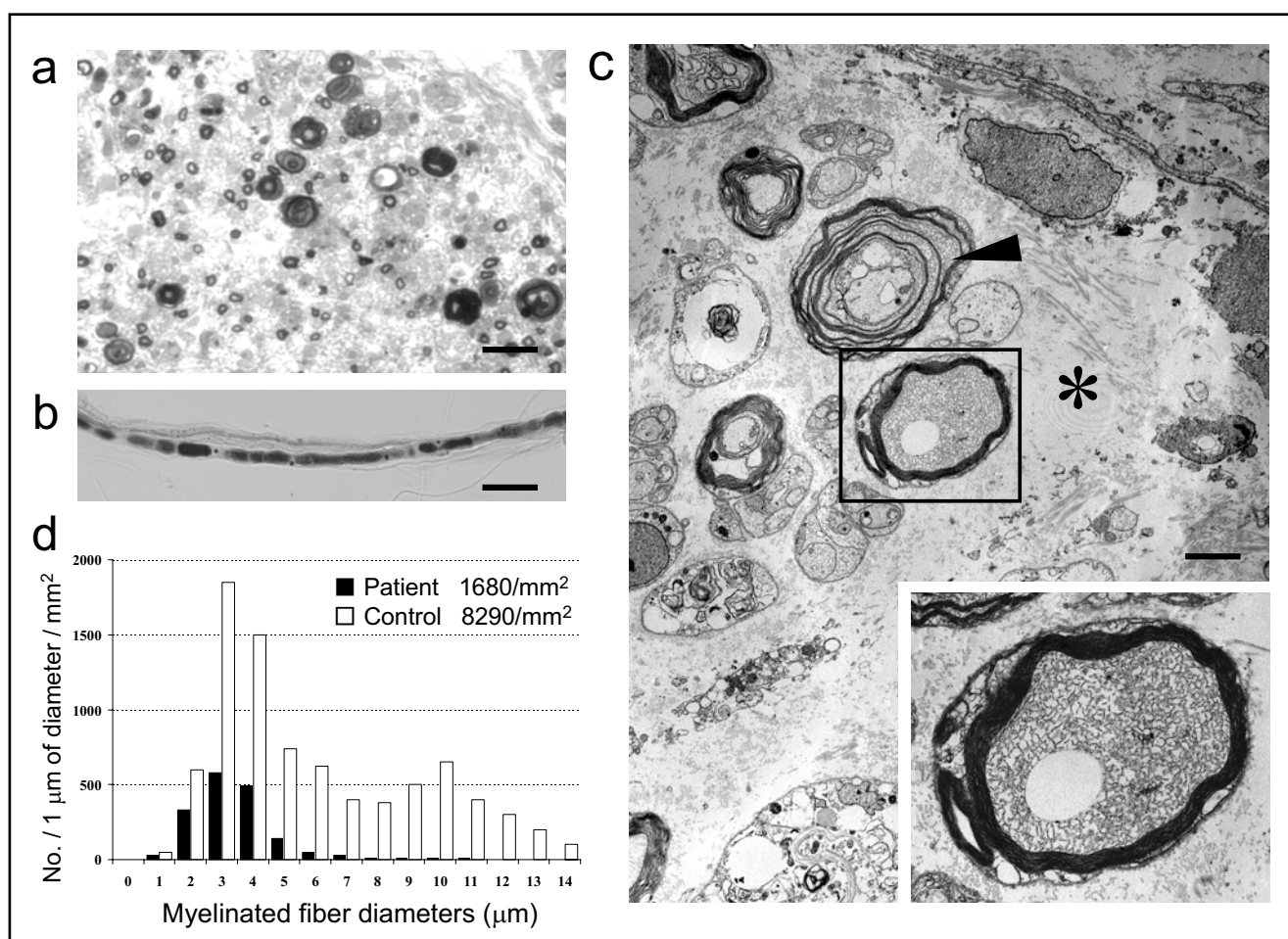
## CASE REPORT

A 29-year-old woman was admitted because of a 2-year-history of slowly progressive distal numbness and weakness in all four extremities, culminating in severe disability. At 12 years of age, hyperthyroidism with diffuse goiter was diagnosed. Treatment with anti-thyroid hormone was administered from 12 to 19 years of age, but was then discontinued on the patient's initiative; the results of medical examinations and the details of treatment were not available for the past 10 years.

On admission, she had general fatigue, palpitations, and hyperhidrosis, which developed over the course of 2 years. She also had a 6-month-history of anorexia nervosa, characterized by bouts of food avoidance and fear of weight gain. The height was 160 cm, and the body weight was 38 kg, decreasing by 7 kg over the past 6

months. The pulse rate was 110/min. Neurologic examination showed distal dominant severe loss of superficial and deep sensations, marked weakness, and areflexia. She presented with markedly decreased bilateral grip strength and difficulty in walking. Cognitive function was normal, with no apparent bladder or rectal dysfunction. Laboratory examinations showed very high levels of free tri-iodothyronine (>20.00 pg/ml; normal: 2.4–4.3) and free thyroxine (>12.00 ng/dl; 0.9–1.8) and a very low level of thyroid-stimulating hormone (<0.03  $\mu$ U/ml; 0.35–3.73) in serum. The serum levels of thiamine and methylcobalamin were within the normal ranges.

Electrophysiologically, complex motor action potential (CMAP) was 1.59 mV (normal range: 9.9–23.0) in the median nerve and 2.07 mV (9.5–20.8) in the ulnar nerve and was not evoked in the peroneal or tibial nerves. Motor nerve conduction velocity was 51.1 m/s



**Fig. 1.** Sural nerve biopsy findings.

**a:** Light microscopic findings of sural nerve specimens stained with toluidine blue. Axonal degeneration with abundant myelin ovoids was accompanied by a marked decrease in myelinated fibers. Fibers with remyelination or onion-bulb formation were not evident.

**b:** Teased nerve analysis showing axonal degeneration with myelin ovoids. Myelinated fibers with short internodes or segmental demyelination were not found.

**c:** Electron microscopic findings of sural nerve specimens. In addition to marked axonal degeneration (magnified image of the square), myelin-sheath dissociation (arrowhead) and edematous changes in the endoneurium (asterisk) were seen. Bars **a** 15  $\mu$ m, **b** 30  $\mu$ m, **c** 2  $\mu$ m.

**d:** Myelinated fiber diameter-frequency histogram of sural nerve. The densities of both large and small myelinated nerve fibers were markedly decreased in our patient. The normal control was age-matched with our patient, and sural nerve specimens were taken from the same site.

(53.0–66.1) in the median nerve and 54.3 m/s (51.0–65.3) in the ulnar nerve. Relatively preserved distal latencies and normal F-wave latencies were revealed. Nerve conduction block was not evident. Sensory-nerve action potentials (SNAPs) of the sural nerve were very low (1.06  $\mu$ V, normal range: 10.0–23.7). SNAPs were not evoked in any other examined nerve. Sensory nerve conduction velocity was 39.0 m/s in the sural nerve. Electromyograms showed neurogenic changes without denervation potentials in all four extremities.

The sural nerve showed axonal degeneration (Figure 1a–c). Semi-thin sections showed frequent myelin ovoid structures. The densities of both large and small myelinated fibers were markedly decreased (Figure 1d). On teased fiber analysis, about 40% of myelinated fibers had axonal degeneration. Ultrastructural examination revealed marked axonal degeneration with myelin-sheath dissociation and edematous changes in the endoneurium.

Antithyroid hormonal therapy was started immediately after admission, and the distal numbness and weakness gradually began to improve. She became able to move independently with normalization of thyroid hormone levels over the course of one month. The serum multivitamin levels one month after admission were as follows: vitamin E, 0.39 mg/dl (0.75–1.41); pyridoxal, 2.6 ng/ml (4.0–19.0); and folic acid, 2.8 ng/ml (3.6–12.9). The patient was therefore given multivitamin replacement therapy. The distal numbness and weakness continued to improve gradually, although the results of nerve conduction studies remained unsatisfactory for several months. The body weight gradually increased by 5 kg over the course of 1 year, and her psychiatric state also improved gradually with normalization of thyroid hormone levels.

## DISCUSSION

We described a patient with untreated hyperthyroidism for 10 years who presented with chronic progressive sensory-motor polyneuropathy. Peripheral nerve involvement developed together with other symptoms of hyperthyroidism from 2 years before presentation. In addition, she had anorexia nervosa and was in poor nutritional status for 6 months. Multivitamin deficiency with decreased levels of vitamin B6, vitamin E, and folic acid was present. Electrophysiological and pathological findings as well as clinical manifestations confirmed the diagnosis of severe axonal polyneuropathy.

Multivitamin deficiency might have been a causal factor in the development of polyneuropathy in our patient, because deficiencies of vitamin B6, vitamin E, and folic acid have each been linked to axonal neuropathy (Windebank 2005). However, the peripheral nerve involvement began to improve substantially only in response to anti-thyroid hormonal therapy before multivitamin replacement. We therefore consider hyperthyroidism to have been another important

causal factor in the polyneuropathy in our patient. To our knowledge, this is the first documented case of chronic severe axonal polyneuropathy associated with hyperthyroidism and complex multivitamin deficiency.

Peripheral nerve involvement is rarely associated with hyperthyroidism (Swanson *et al.* 1981; Duyff *et al.* 2000; Pandit *et al.* 1998; Szollar *et al.* 1988). A recent study reported that 4 of 21 patients with untreated hyperthyroidism had electrophysiologic evidence of mild axonal degeneration (Duyff *et al.* 2000). Weakness in all four patients never exceeded grade 4 paresis on manual muscle testing, in contrast to the marked weakness in our patient. Chronic axonal polyneuropathy associated with hyperthyroidism and pathologically confirmed axonal degeneration has not been reported previously, although two patients with acute thyrotoxic polyneuropathy such as Basedow's paraplegia have been described (Pandit *et al.* 1998; Szollar *et al.* 1988). Pathologically, our patient showed much more severe axonal changes and more markedly decreased myelinated fibers than the two previous patients with acute disease. Our patient might have had a very rare subtype of polyneuropathy associated with hyperthyroidism as well as multivitamin deficiency.

Although our patient had deficiencies of vitamin B6, vitamin E, and folic acid, complex deficiencies of these vitamins are very rare. Hypermetabolism due to hyperthyroidism might have accelerated the depletion of vitamin stores. In fact, hyperthyroidism was reported to be associated with deficiencies of vitamin E and folic acid in a hypermetabolic state (McGowan & Bartuska 1974). In addition, the patient's history of anorexia nervosa and self-imposed dietary restriction might also have contributed to the multivitamin deficiency. In fact, untreated hyperthyroidism is occasionally accompanied by anorexia nervosa (Rolla *et al.* 1986). The incidence of psychosis in hyperthyroidism was previously reported to be 20% (Jadresic 1995). Some patients with anorexia nervosa use weight-losing intercurrent illness to justify weight loss, such as the untreated hyperthyroidism in our patient. This factor probably also contributed to vitamin-store depletion. Therefore, thyroid function should be evaluated in patients with anorexia nervosa who present with neuropathy.

The severe axonal sensory-motor polyneuropathy in our patient was thus probably caused by hyperthyroidism and multivitamin deficiency with anorexia nervosa. Consequently, multivitamin replacement as well as anti-thyroid therapy was essential. Our findings strongly suggest that not only multivitamin deficiency but also hyperthyroidism can cause axonal polyneuropathy, thus expanding the clinical spectrum of hyperthyroidism. However, clinical or pathological studies of similar cases are needed to draw firm conclusions.

### Disclosure

*The authors have no financial interest in this manuscript and no affiliations to disclose.*

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