Transient hypothyroidism induced by anticonvulsant agents

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Abstract

The question whether antiepileptic drugs alter thyroid function requires a better understanding. In our article, we report two sisters, one of whom was treated with levothyroxine because of hypothyroidism. Although both women received anticonvulsant therapy, transient hypothyroidism was observed only in the hypothyroid woman and was found after treatment with classic anticonvulsant agents (carbamazepine and sodium valproate) but not with gabapentin. Our report shows that the effect of anti-epileptic drugs on the thyroid gland depends on the patient's hormonal status and on the drug being used.

CASE REPORT

INTRODUCTION

The question whether anticonvulsant agents affect thyroid function is far from being fully understood. Some authors observed that classic antiepileptic drugs, including carbemazepine, oxcarbazepine and valproic acid, reduced thyroid hormone levels (Haugen 2009; Betteridge & Fink 2009; Steinhoff 2006). It is possible that they may also affect thyroid function by altering pituitary thyrotrope responsiveness to hormonal feedback and inducing central hypothyroidism (Haugen 2009). In turn, other authors did not find such a relationship (Verrotti *et al.* 2008). The following factors may contribute to the study-dependent effects of anticonvulsant agents on thyroid function: different inclusion criteria, drug- and dose-related differences, differences in the duration of treatment and/or methodological differences. Our case report shows for the first time that the effect of anti-epileptic drugs on the thyroid gland depends on the patient's hormonal status and on the drug being used.

CASE PRESENTATION

The first health problems in our patient appeared at the age of 29, when she underwent subtotal thyroidectomy because of multinodular goiter without any histologic evidence for malignant disease. As a result, she had to receive levothyroxine at dose of 100 μg daily. For the following 11 years she was free from symptoms of thyroid hormone deficiency or excess, while her TSH and free thy-

roid hormone levels were within the reference range, and therefore she did not require any changes in the dosage of this agent. At the age of 39, she developed trigeminal neuralgia and was prescribed by a consultant neurologist to take carbamazepine (200 mg three times a day). Although this treatment reduced pain intensity and frequency, after 30 days of the treatment she started to complain of symptoms suggestive of hypothyroidism (fatigue, muscle cramping, weight gain, constipation, cold intolerance, dry skin and menstrual irregularities). On admission, physical examination showed coarse facial features, periorbital puffiness, dry skin, slight bradycardia, hyporeflexia with delayed relaxation and low body temperature (36.2 °C). Her TSH levels were elevated (35.4 U/L, reference range: 0.4–4.3) while free thyroid hormone reduced (free thyroxine - 7.5 pmol/L, reference range: 12.0–22.0; free triiodothyronine - 2.2 pmol/L, reference range: 2.8–6.0). Thyroid peroxidase antibodies were negative. To improve her clinical condition and normalize TSH and thyroid hormone levels, the dose of levothyroxine had to be gradually increased to 150 µg daily. After 12 weeks, carbamazepine treatment was terminated and soon afterwards some symptoms of mild hyperthyroidism occurred, which were accompanied by a decrease in TSH levels (0.003 mU/L) and an increase in free thyroid hormone levels (free thyroxine - 24.3 pmol/L; free triiodothyronine - 11.2 pmol/L) and therefore the daily dose of levothyroxine was reduced to 100 µg. Two years later, trigeminal neuralgia reappeared and the patient again received carbamazepine treatment, but at a higher dose (900 mg daily) than previously, and after the following 6 weeks she developed hypothyroidism. Her clinical symptoms, although similar to those noticed previously, were, however, more severe and only the dose of 200 µg of levothyroxine daily effectively normalized both her clinical condition and hormonal abnormalities. Carbamazepine treatment was continued for 12 weeks and terminated. Two months after carbamazepine treatment termination, the patient started to experience hyperthyroidism (of higher intensity than 2 years before) and required the reduction of levothyroxine dose to 100 µg daily. Two following periods of trigeminal neuralgia exacerbation took place 11 and 23 months later. Because the patient was outside our area, she did not contact our clinic. Instead, each time she received sodium valproate treatment at different daily doses (900 and 1 200 mg, respectively). During the periods when she received sodium valproate, the daily requirements of levothyroxine were markedly increased (150 µg and 175 µg), and after cessation of the treatment each time fell to 100 µg. The last time when our patient developed trigeminal neuralgia was 2 years ago. Instead of carbamazepine and sodium valproate, she was prescribed with gabapentin (1 200 mg/daily), being a drug with a negligible effect on the P450 system (Tanaka 1999). This treatment, not only effectively reduced pain intensity, but was also devoid of any effect on thyroid function and therefore levothyroxine dose remained constant.

We also investigated thyroid function in the patient's younger (38-year old) sister, who for 10 years had been treated with high doses of oxcarbazepine (1 800 mg) because of epilepsy. However, no differences in plasma TSH (1.85 mU/L) and free thyroid hormones (free thyroxine - 14.3 pmol/L, free triiodothyronine - 5.2 pmol/L) were observed when compared her present thyroid function with thyroid function assessed 10 years earlier (TSH - 1.92, free thyroxine - 14.1 pmol/L, free triiodothyronine - 5.6 pmol/L).

DISCUSSION

The association between treatment with anticonvulsant agents and a decrease in thyroid hormone levels in the index patient was not accidental. Hypothyroidism developed each time when patient received carbamazepine and sodium valproate and resolved after termination of this treatment. Moreover, the dose of levothyroxine required for the normalization of thyroid hormone function was proportional to the applied dose of carbamazepine and sodium valproate. Furthermore, in the period between attacks, when the patient did not receive any anticonvulsant drugs, the daily dose of levothyroxine was the same as before the first attack. Although, it cannot be fully excluded that a deterioration in thyroid function was secondary to the non-specific effect of pain treatment on the hypothalamic-pituitary-thyroid axis, this explanation seems to be rather unlikely. Hypothyroidism did not occur when our patient received gabapentin, despite its similar clinical effectiveness in the treatment of trigeminal neuralgia to that of carbamazepine and sodium valproate. Interestingly, no changes in thyroid status were observed in the patient's sister was treated for many years with a relatively high dose of oxcarbazepine because of epilepsy. This probably indicates that hypothyroidism easier develops in patients in whom the thyroid gland is unable to increase thyroid hormone production in response to increased thyroid hormone metabolism in the liver. Because both carbamazepine and sodium valproate are strong inducers of the hepatic P450 system (Johannessen Landmark & Patsalos 2010), it seems that hypothyroid subjects requiring thyroid hormone supplementation should be treated with antiepileptic agents which do not have any impact or, at most, have only a minimal impact on the hepatic P450 system.

Conflict of interest statement: *The authors declare that there is no conflict of interest.*

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