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SPECIAL REPORT

Venous thromboembolism in overt hyperthyroidism – a direct association with clinical implications?

L.P.B. Elbers[1,2]*, B. van Zaane[1,2], V.E.A. Gerdes[1,2], J.M. Coutinho[3], P.H. Bisschop[4], E. Fliers[4]

[1]Department of Internal Medicine, Slotervaart Hospital, Amsterdam, the Netherlands, Departments of [2]Vascular Medicine, [3]Neurology, [4]Endocrinology and Metabolism, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands, *corresponding author: tel.: +31 (0)20-5125194, fax +31 (0)20-5124783, e-mail: l.p.elbers@amc.uva.nl

ABSTRACT

Hyperthyroidism is associated with procoagulant changes in the haemostatic system. At present, it is uncertain whether this leads to an increased risk of venous and/or arterial thrombosis. Only a few small studies have investigated this association but due to methodological limitations it is not possible to draw any definitive conclusions at this stage. Here we report two patients with severe venous thromboembolism (VTE) and concomitant hyperthyroidism without any risk factors for VTE. Hereby, we emphasise a possible association as supported by a number of previous studies. In a planned prospective multicentre cohort study we will examine the association between hyperthyroidism and VTE and determine its clinical relevance.

KEYWORDS

Hyperthyroidism, venous thromboembolism, pulmonary embolism, sinus thrombosis

INTRODUCTION

Hyperthyroidism is associated with potential procoagulant changes in the haemostatic system.[1-3] It is uncertain whether this also leads to an increased risk of venous and/or arterial thromboembolism. A gradual rise in venous thromboembolism (VTE) risk with increasing levels of free thyroxine within the reference range has been reported,[4] but thus far only four small studies have directly investigated the association between overt hyperthyroidism and VTE.[5-8] The contradictory results of these studies may – at least in part – be due to methodological differences and limitations. In a retrospective study, 5 out of 587 patients with hyperthyroidism experienced a VTE during the study period of nine months, resulting in an incidence rate of 8.7 per 1000 person-years, which is higher than in the general population.[5] Another retrospective study identified a similar incidence rate[6] and Lin *et al*. found a 2.3-fold risk of pulmonary embolism (PE) during a five-year follow-up period in patients with hyperthyroidism compared with a comparison cohort.[7] By contrast, another study could not detect an increased risk of VTE in hyperthyroidism.[8]
Here, we report two patients with severe hyperthyroidism who suffered from venous thrombosis. One had cerebral venous thrombosis of the left transverse sinus, while the other patient was diagnosed with multiple pulmonary embolisms in the upper and lower lobe of the right lung.

CASES

A 50-year-old woman with an unremarkable medical history was admitted with severe hyperthyroidism. She was confused, which was initially attributed to the hyperthyroidism, and suffered from vomiting and headache. Physical examination revealed a diffuse goitre. On neurological examination, she had a normal consciousness, was aphasic, had a right-sided hemianopia, and a mild paresis of the right arm. Laboratory tests showed severe thyrotoxicosis (TSH <0.01 mE/l and FT4 >100 pmol/l; reference range TSH 0.25-4.0 mU/l and FT4 11.0-22.0 pmol/l) due to Graves' disease (T.B.I.I. 29.9 E/l and anti-TPO >3000 kU/l). ECG showed a sinus rhythm. A CT scan of the brain revealed a large left-sided temporo-parietal haemorrhagic infarct with mass effect and a midline shift of approximately 5 mm (*figure 1*). MRI/MRV showed absence

of flow in the left transverse and sigmoid sinus, consistent with a diagnosis of cerebral venous thrombosis (*figure 2*). Low-molecular-weight heparin was started in a therapeutic dose. During admission she suffered from focal epileptic seizures, which were treated with clonazepam and valproic acid. The hyperthyroidism was treated with potassium iodide drops 1.6 ml 3 times a day, propranolol 40 mg 4 times a day and propylthiouracil 200 mg 6 times a day. Her clinical situation improved, obviating the need for neurosurgical intervention. The heparin was switched to a vitamin K antagonist which she used for a total of 18 months. Three weeks after admission she was discharged on valproic acid, hydrocortisone, propranolol and propylthiouracil. After discharge her aphasia improved but she repeatedly suffered from epileptic seizures which were successfully treated with phenytoin, lamotrigine and clobazam.

The second case was a 46-year-old woman who presented with a fever, productive cough, haemoptysis and painful breathing during the last couple of days. In the previous weeks she had noticed swelling and redness of her left leg which had spontaneously resolved. She had a history of Graves' disease treated with thiamazole 30 mg once a day and levothyroxine 100 µg once a day for the last year. She had been on amoxicillin for four days. No risk factors for venous thrombosis were present. On physical examination she had a breathing frequency of 30 per minute, a temperature of 38.6 °C and a pulse rate of 115 beats per minute. CT scanning showed multiple segmental pulmonary emboli in the right upper and lower lobe with infarctions of the right lung. The patient was treated with low-molecular-weight heparin and a vitamin K antagonist was started. Laboratory tests three days prior to presentation showed a TSH of 0.01 mE/l and FT4 of >70 pmol/l (reference range TSH 0.05 -5.00 mE/l and FT4 10.0-23.0 pmol/l). It appeared that she had not used her block-and-replacement therapy.

DISCUSSION

By presenting these two cases, our aim is to emphasise the possibility that hyperthyroidism is a risk factor for VTE, as indicated previously by a small number of retrospective studies. Neither of these patients had any identifiable risk factors for VTE and both were relatively young. Until now, four small retrospective studies have investigated the association between hyperthyroidism and VTE[5-8] but due to methodological limitations we cannot draw any firm conclusions at this stage. So at present, the available literature does not provide us with answers to our main questions: is the risk of VTE during hyperthyroidism high enough to classify such VTE as provoked, thereby diminishing the need for prolonged anticoagulant therapy? And, does VTE in hyperthyroid patients mainly occur prior to the start of antithyroid agents? If this is true, VTE should be considered a possible first presentation of hyperthyroidism and thromboprophylaxis in patients with hyperthyroidism may not be very effective.

In order to gain more insight into the relationship between hyperthyroidism and VTE, we intend to carry out a prospective multicentre cohort study among 4000 patients with newly diagnosed overt hyperthyroidism. Our aim is to quantify the incidence rate of VTE, myocardial infarction, ischaemic stroke and atrial fibrillation during overt hyperthyroidism and compare this with the rate in a control population.

In summary, we emphasise the possibility that hyperthyroidism is a risk factor for VTE as suggested by a number of previous studies. We address this issue by

Figure 1. *Axial CT of the brain showing a large parieto-temporal haemorrhagic infarct on the left side*

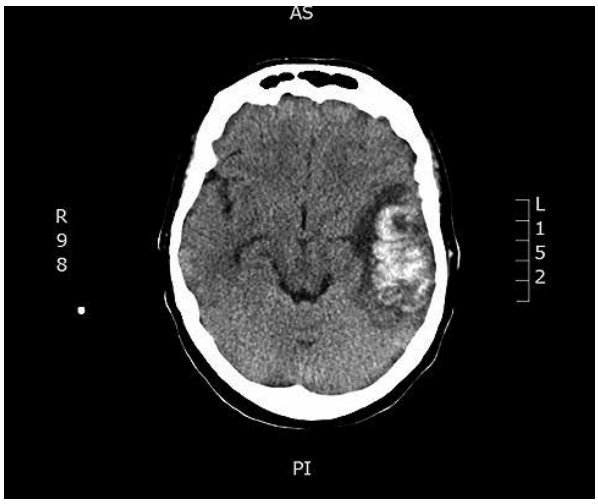
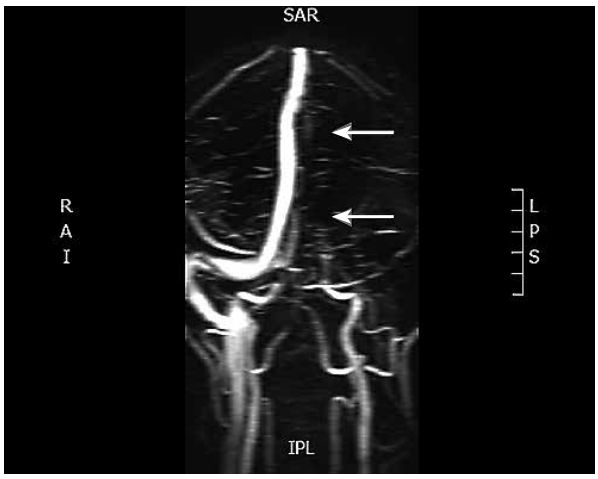


Figure 2. *Magnetic resonance venography of the cerebral sinuses showing absence of flow in the left transverse and sigmoid sinuses and the internal jugular vein*



reporting two patients with severe VTE and concomitant severe hyperthyroidism without any risk factors for VTE. In a planned prospective multicentre cohort study we will examine the association between hyperthyroidism and VTE and determine its clinical relevance.

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DISCLOSURES

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