Cerebral Venous Thrombosis and Hyperthyroidism

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Abstract

Cerebral venous thrombosis (CVT) is mostly caused by pro-thrombotic factors. Hyperthyroidism is not a well-known risk factor. We present a case report on a 17-year-old girl who developed life-threatening CVT after Graves’ disease. A review of the literature reveals further 34 cases of CVT and hyperthyroidism. Abnormalities in the coagulation system leading to hypercoagulability such as increased coagulation factors are detected in patients with hyperthyroidism, and these abnormalities seem to be thyroxin-dependent. The cause of CVT may be multi-factorial. Our patient used oral hormonal contraception without complications until the development of severe Graves’ disease. Hyperthyroidism is suspected as the main precipitating cause of CVT in this case. We recommend performing MRI with venous angiography when a hyperthyroid patient presents with unusual headache alone or in combination with other neurological symptoms. If CVT is proven, blood screening for coagulation abnormalities should be performed. On the other hand, diagnostics for finding the cause of CVT should include blood tests of thyroid function. Early treatment of CVT and hyperthyroidism is mandatory.

Introduction

Cerebral venous thrombosis (CVT) represents only about 0.5-1 % of all strokes [1]. The incidence is estimated to be 2-4 per million per year, but the number is probably higher due to undiagnosed cases [1,2]. CVT occurs most often in the 3rd decade of life and then affects mostly women, but among children and elderly patients there is no difference concerning sexes [1].

CVT has the best prognosis at a young age without severe neurological deficits, such as hemiparesis, epileptic seizures and coma, or other co-morbidity such as cancer and serious infection [3]. A prospective multi-center study showed that 75% of patients with CVT were women with a mean age of 34 years and the best prognosis was found for women with risk factors like hormonal contraception, pregnancy and maternity [4].

Pro-thrombotic causes are found in about 85% of patients with CVT and include hormonal, genetic and acquired hematologic, inflammatory or immunologic causes, infections, cancer and other specific causes while about 15% are considered to be idiopathic [5].

Symptoms of CVT are usually increasing headache, blurred vision and acute focal neurological disturbances of function, such as paresis and focal seizures. Magnetic resonance imaging (MRI) with venous angiography is the gold standard for the diagnosis of CVT and is superior to computer tomography (CT), which is found negative in 10-30% [6].

Symptoms of Graves’ disease are goiter, exophthalmos and ophthalmopathy (staring eyes) and skin changes, such as pre-tibial myxedema with thickened, orange-skin similar areas which are itching or hyper pigmented. Muscle weakness, weight changes, tremor, perspiration, nervousness, irritability, intolerance to heat, tachycardia and atrial fibrillation are symptoms that may occur due to Graves’ disease or other hyperthyroidism [7].

Hyperthyroidism is not a well-known risk factor for CVT. Our case report is a young woman who developed life-threatening CVT after Graves’ disease. We have further reviewed the literature concerning CVT and hyperthyroidism.

A 17-year-old girl, non-smoker, had used the hormonal contraception Mercilon (150 µg desogestrel and 20 µg etinylestradiol) for two years without any medical problems. After several weeks of irritability, tiredness, weight-gain, intolerance to heat, slight diarrhea, development of goiter and itching pre-tibial myxedema, Graves’ disease was diagnosed with free thyroxin (FT4) 8.39 pmol/l (reference 12.6-21.0), TSH <0.01 mU/l (reference 0.51-4.3) and thyroid-receptor antibodies >40 IU/l (reference <1.5). After start of treatment with carbimazole she was discharged from the hospital, but on the same day she developed right occipital headache, pain in the neck and nausea. Four days later, she had a transient hemiparesis and focal seizures in her left hand. On the fifth day she was admitted to our department after recurrent and persisting left hemiparesis and lost consciousness due to generalized seizures. Her pupils were dilated, not reacting to light and Glasgow Coma Scale score at admittance was 3 points. She was intubated and propofol-narcosis was started due to no response to diazepam. MRI showed extensive thrombosis in the sagittal sinus, the right transverse sinus, the sigmoid sinus and the proximal right jugular vein (Figures 1 and 2) with venous infarction (Figure 3) in the right parietal region. Two minor bleedings were present in the right temporal lobe because of stasis (Figure 4). The left sinus transversus was atretic. She was treated with dalteparin, adjusted after anti-factor-X a measurements in plasma, four hours after the last injection with the level-aim between 0.6-1.0 IU/ml (reference 0.00-0.01). She slightly recovered over weeks, but developed significant bilateral exophthalmos. Anti-thrombin,
were women. Graves’ disease was present among 21 of the 35 patients and 17 of these were women.

Discussion

The predominance of women and young age are compatible with results of other studies of CVT [3] and earlier review articles about CVT and hyperthyroidism [30,36]. The prevalence of CVT is 1.7% for thyroid morbidity, 34.1% for pro-thrombotic conditions (antithrombin III deficiency, protein-S- or protein-C deficiency, antiphospholipid syndrome, activated protein-C resistance, factor V Leiden mutation, pro-thrombin G20210A mutation) and 53.3% for use of oral hormonal contraception [37]. However, as the overview is only listing case studies, it is not possible to draw conclusions about frequency of coagulation deficiencies, infections or the use of oral contraception as blood samples were not standardized screened and cases were not standardized reported.

Review of the Literature

In addition to our patient, we found 34 other cases of CVT and hyperthyroidism (Table 1). The mean age is 32 years. The youngest patient was an eight year old girl and the oldest patient a 60 year old man. Five of the 35 patients were older than 40 years and 22 patients

Figure 1: T1-weighted 3D-volume imaging with contrast (slide thickness 1.1 mm, TR 2020 ms, TE 3.93 ms) shows filling defects consistent with thrombosis in the superior sagittal sinus and in the right transverse sinus (arrows).

Figure 2: T1-weighted 3D-volume imaging with contrast (slide thickness 1.1 mm, TR 2020 ms, TE 3.93 ms) shows filling defects consistent with thrombosis in the superior sagittal sinus and in the right transverse sinus (arrows).

Figure 3: Diffusion Weighted Imaging (b1000) (slide thickness 5 mm, TR 3200 ms, TE 94 ms) shows venous infarction in the right parietal lobe.

Figure 4: Susceptibility Weighted Imaging (SWI) (slide thickness 2 mm, TR 50 ms, TE 40 ms) shows hemorrhagic lesions in the right temporal lobe (asterisks) and accented vein drawings due to stasis.
Hyperthyroidism and the coagulation system

Several studies of patients with hyperthyroidism have shown increased incidence of venous thromboembolic events [38], such as pulmonary embolism [39] and deep venous thrombosis [40]. Abnormalities in the coagulation system, such as increased fibrinogen, von Willebrand factor (vWF), Plasminogen activator inhibitor 1 (PAI-1), coagulation factors VIII, IX and X and shorter activated partial thromboplastin time (APTT) have been found in hyperthyroid patients compared with euthyroid controls [41]. In a follow-up study, healthy volunteers were given levothyroxin and it was proved increased levels of fibrinogen, vWF, PAI-1 and coagulation factors VIII, IX and X [42]. These findings indicate that hypercoagulability and decreased fibrinolysis in hyperthyroidism is thyroxin-dependent.

A case study that supports the hypothesis of hypercoagulability reported death from CVT caused by thyroid crisis [25]. Another patient, also with life-threatening CVT and thyroid crisis, was treated with plasmapheresis which led to rapid reduction of fT3 and fT4 and removal of anti-phospholipid antibodies, with significant clinical improvement and normalization of factor VIII and vWF [29].

Other risk factors for CVT?

Our patient had heterozygous methylenetetrahydrofolat reductase (MTHFR) gene. MTHFR mutation gene defects may lead to hyperhomocysteinemia. The prevalence of MTHFR mutations is found to be 14% but is only of clinical relevance when the gene is homozygote [44] and a case study reports compression of truncus brachiocephalicus (APC-R) [28].

Mechanical compression of veins from goiter has been mentioned [44] and a case study reports compression of truncus brachiocephalicus from goiter [45]. However, this was not suspected in our patient. It is not suspected that carbimazole increases the risk of venous thromboembolism [46].

Our patient had no problems tolerating a combination of desogestrel and ethinylestradiol before the development of Graves’ disease. Some

<table>
<thead>
<tr>
<th>First author, published year (reference)</th>
<th>Age/ Gender</th>
<th>Type of hyperthyroidism</th>
<th>Coagulation deficiency and other risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schutta, 1991 [8]</td>
<td>34/M</td>
<td>Thyrotoxicosis</td>
<td>Plasminogen deficiency, thrombocytosis,</td>
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<tr>
<td>Sitburn, 1996 [10]</td>
<td>18/F</td>
<td>Thyrotoxicosis</td>
<td>Active protein C-resistance (APC-R)</td>
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<td>De Schryver, 1999 [12]</td>
<td>32/M</td>
<td>Thyrotoxicosis</td>
<td>Increased factor VII</td>
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<tr>
<td>Verbeeck, 2000 [13]</td>
<td>28/F</td>
<td>GD</td>
<td>None mentioned</td>
</tr>
<tr>
<td>Dai, 2000 [14]</td>
<td>39/F, 38/M</td>
<td>Hypercoagulopathy</td>
<td>None mentioned</td>
</tr>
<tr>
<td>Longe, 2000 [15]</td>
<td>18/M, 18/F</td>
<td>Hypercoagulopathy</td>
<td>None mentioned</td>
</tr>
<tr>
<td>Ra, 2001 [16]</td>
<td>60/F</td>
<td>GD</td>
<td>Protein C deficiency, increased fibrinogen</td>
</tr>
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<td>Molloy, 2003 [18]</td>
<td>28/F, 32/F</td>
<td>GD</td>
<td>Heterozygous factor V Leiden mutation</td>
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<tr>
<td>Colleran, 2003 [19]</td>
<td>37/F</td>
<td>GD</td>
<td>None mentioned</td>
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<td>Madronero-Vuelta, 2004 [20]</td>
<td>42/F</td>
<td>De Quervains thyroiditis</td>
<td>Heterozygous pro-thrombin G20210A mutation</td>
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<td>Karouache, 2004 [21]</td>
<td>38/F, 44/F</td>
<td>GD</td>
<td>None mentioned</td>
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<td>Mouton, 2005 [22]</td>
<td>32/F, 49/F</td>
<td>Postpartum thyroiditis</td>
<td>Increased factor VII</td>
</tr>
<tr>
<td>Kasuga, 2006 [23]</td>
<td>39/F, 50/F</td>
<td>GD</td>
<td>Increased factor VIII, APC-R</td>
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<tr>
<td>Roch, 2006 [24]</td>
<td>25/F</td>
<td>GD</td>
<td>Increased factor VIII</td>
</tr>
<tr>
<td>Kim, 2008 [26]</td>
<td>23/F</td>
<td>GD/ thyrotoxicosis</td>
<td>Increased factor VIII</td>
</tr>
<tr>
<td>Pekdemir, 2008 [27]</td>
<td>28/M</td>
<td>Hypercoagulopathy</td>
<td>None mentioned</td>
</tr>
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<td>Strada, 2008 [28]</td>
<td>29/F, 25/F</td>
<td>Thyrotoxicosis</td>
<td>Elevated homocysteine, homozygous MTHFR C677Tgene</td>
</tr>
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<td>Usami, 2009 [29]</td>
<td>34/F</td>
<td>Thyrotoxicosis</td>
<td>Gastroenteritis and dehydration, increased factor VIII, protein C deficiency, anti-phospholipid antibodies positive</td>
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<tr>
<td>Hermans, 2011 [31]</td>
<td>22/F</td>
<td>GD</td>
<td>None mentioned</td>
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<td>Knudsen-Baas, 2012</td>
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<td>GD</td>
<td>Heterozygous MTHFR gene</td>
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<td>Hwang, 2012 [33]</td>
<td>31/M</td>
<td>Hypercoagulopathy</td>
<td>Increased factor IX and XI</td>
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<td>Merino, 2012 [34]</td>
<td>30/M</td>
<td>Hypercoagulopathy</td>
<td>Increased factor VIII and von Willebrand factor Ag</td>
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<tr>
<td>Migeot, 2013 [35]</td>
<td>26/F</td>
<td>GD</td>
<td>Post-partum, increased factor VIII</td>
</tr>
</tbody>
</table>

Table 1: Overview of published cases from 1991 to 2013 of patients with cerebral venous thrombosis and hyperthyroidism.

of the other cases in the literature with hyperthyroidism and CVT were certainly not caused by hormonal contraception as twelve patients were men and one of the females was eight years old. A Danish cohort study of more than 1.6 million women found low risks of thrombotic stroke and myocardial infarction with hormonal contraception, although there were slight differences concerning components and dosages [47]. It is possible that use of hormonal contraceptive contributed to the CVT in our patient, but we suspect Graves’ disease as the main cause.

Conclusions

The cause of CVT may be multi-factorial. A review of the literature shows several cases of CVT due to hyperthyroidism. Studies indicate that a high thyroxin level causes a hypercoagulable condition. We suspect severe Graves’ disease as the main precipitating cause of life-threatening CVT in a 17 year old girl with previously uncomplicated use of hormonal contraception. CVT should be suspected and MRI or in combination with neurological deficits occurs in patients with hyperthyroidism. In case of CVT, blood screening for coagulation abnormalities is indicated. On the other hand, hyperthyroidism should be suspected in young patients with CVT. CVT and hyperthyroidism must be treated as soon as possible.

References


