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Hyperthyroidism with increased factor VIII procoagulant protein as a predisposing factor for cerebral venous thrombosis

Cerebral venous thrombosis (CVT) is a rare disorder, with an incidence of approximately 4/1 000 000 per year, occurring more frequently in women than in men (ratio of 1.29:1).¹ CVT is a multifactorial condition, known predisposing factors include venous stasis, hypercoagulability, vasculitis, systemic lupus erythematosus, and trauma. Mortality after CVT ranges from 5% to 30%.¹ The optimal treatment consists of anticoagulation for six months and should only be maintained beyond this time if known risk factors for CVT persist. Treatment should not be discontinued in case of an asymptomatic haemorrhagic transformation of the associated venous infarct.²

In recent years, a few thyrotoxic patients with CVT have been reported. An association between hyperthyroidism and increase of FVIII has also been described,³ and recent data suggest an increased incidence of venous thrombosis in patients with hyperthyroidism and high FVIII levels.⁴ Here we report a patient with increased FVIII levels and an autoimmune hyperthyroidism, who developed a CVT complicated by venous infarction.

Case report

A 39 year old woman was admitted to the emergency room after a brief episode of convulsions, preceded by a short period of perseveration, verbal aggressiveness, and disorientation. Four days before admission, she had developed a sudden, pulsatile left sided headache, which was unresponsive to paracetamol and ibuprofen. Personal and family medical histories were unremarkable. She had been taking oral contraceptive medication for several years and smoked two cigarettes a day. Neurological examination was normal, except for a temporary confusional state that lasted less than 24 hours. Electroencephalography demonstrated a slow arrhythmia in the left temporal region, without epileptic activity. Brain computed tomography revealed a left temporal hypodense lesion, with moderate contrast enhancement. Magnetic resonance imaging of the brain performed 24 hours later, showed a non-specific hyperintense lesion on the T1 weighted images. The magnetic resonance venography (fig 1) revealed an extensive thrombosis of the left lateral sinus with involvement of the distal part of the jugular vein. The diagnosis of a temporal venous infarct was made. Treatment with unfractionated heparin was started

promptly and maintained for one week, followed by oral anticoagulation with an INR between 2 and 3. Oral contraceptive treatment was discontinued and the patient was advised to stop smoking. Extensive screening for coagulopathies including antiphospholipid syndrome, dysfibrinogenemia, deficiencies in antithrombin, protein C and S, hyperhomocysteinaemia, and activated protein C resistance revealed no abnormalities. The G20210A prothrombin gene mutation was absent. Autoimmune tests including ANF, ANCA, complement and rheumatoid factors were negative. Further analysis revealed a state of hyperthyroidism with a TSH value below 0.015 mIU/l (normal: 0.27-4.2), free triiodothyronin of 12.1 ng/l (normal: 9.3-18.0 ng/l), and an increased free thyroxin of 28.8 ng/l (normal: 9.3-18.0 ng/l). Anti-TSH receptor antibodies were found consistent with Graves-Basedow's disease. The patient was treated with thiamazole (3x10 mg/day), followed by the administration of radioactive iodine (9 mCi). One month after discontinuation of oral contraceptives, thyroid tests remained increased. FVIII procoagulant protein showed a marked increase: 1680 IU/l (normal levels: 500-1500 IU/l) and remained slightly raised five weeks later. Meanwhile the patient developed a hypothyroidism, necessitating a substitution treatment with LT4. After a further six months both thyroid tests and FVIII levels normalised and anticoagulants were stopped.

Discussion

Increase of clotting FVIII occurs in several conditions such as strenuous exercise, fever, pregnancy, renal failure, adrenaline (epinephrine) infusion, prednisone treatment, and intravascular haemolysis.³ Hyperthyroidism, whatever its origin, also induces a significant increase in FVIII levels, with a comparatively short activated partial thromboplastin time, while other clotting factors remain within normal limits.³ Moreover, correction of thyroid function results in a normalisation of FVIII levels. In patients with recurrent hyperthyroidism, levels of FVIII are known to fluctuate with thyroid function. The physiopathological mechanism involved remains unclear. Excessive adrenergic activity occurring in hyperthyroid patients could have a direct effect on the production of FVIII. The fact that administration of propranolol inhibits the increase of FVIII in patients with hyperthyroidism supports this theory.

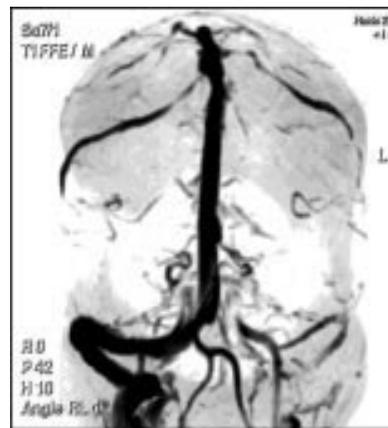


Figure 1 Magnetic resonance venography confirms complete occlusion of the left lateral sinus.

In 1995 a large study was performed on 301 case-control pairs, younger than 70 with a first episode of deep vein thrombosis.⁴ Patients with malignant disorders were excluded. The authors showed that high levels of FVIII contribute to the development of venous thrombosis in a dose dependent manner. In multivariate analysis FVIII concentrations above 1500 IU/l result in a 4.8-fold higher risk of developing venous thrombosis. It was also shown that this is not an acute phase reaction, and that high levels of FVIII persist for months after the thrombotic event. Recently, it was calculated that the reported incidence of CVT and hyperthyroidism is significantly higher than expected by chance alone.³ A small number of case reports mention the concomitant occurrence of thyrotoxicosis and CVT. To our knowledge, this is the first reported case of CVT of the left lateral sinus associated with clinically silent hyperthyroidism and increased FVIII levels. Correction of thyroid function resulted in normalisation of FVIII levels. This report emphasises the need for thyroid evaluation in every patient with CVT and other venous thromboembolic events, even in the absence of clinical signs of hyperthyroidism. Every patient with hyperthyroidism, especially if immobilised, has a significantly higher risk of developing venous thromboembolism and should benefit from maximal preventive measures.

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Coma with focal neurological signs caused by *Datura stramonium* intoxication in a young man

Intoxication with *Datura stramonium*, which contains a variety of tropane alkaloids, produces atropine-like effects. The seeds of *D stramonium* (semen scopolii) in particular contain hyoscyamine, scopolamine, and atropine. Symptoms include agitation, disorientation, hallucination, flushed skin, dilatation of

pupils, urine retention, seizures, and respiratory depression.¹ *D stramonium* is voluntarily used for its hallucinogenic properties.² Its anticholinergic compounds are likely to produce delirium and stupor but rarely cause deep coma.³

A common diagnostic error is to mistake coma resulting from brainstem infarction, supratentorial mass lesions, metabolic disorders, or hypoxia for coma resulting from poisoning. The initial distinction of these conditions may be difficult.⁴ We report an unusual case of *D stramonium* intoxication in a patient who initially presented with deep coma, focal neurological signs, and decorticate posture.

A 30 year old male patient was admitted to an emergency unit for acute loss of consciousness. The accompanying person reported that the patient had had a few beers and then suddenly fell on his back. He was unconscious and awoke for a few seconds but shortly afterward lost consciousness again and remained in a stiff position and unconscious until admission.

The first neurological examination was performed one and a half hours after the sudden onset of symptoms. There was no evidence of trauma. Vital signs, such as cardiopulmonary function, body temperature, and blood oxygenation, were normal. Initial laboratory testing for electrolyte disorders, renal or hepatic failure, and hypoglycaemia or hyperglycaemia found no major pathology. Blood alcohol concentration was 1.1‰.

Neurologically, he presented in a decorticate posture. The upper limbs were in a paratonic flexor position with increase of flexion tonus to noxious stimuli, which was more pronounced on the right side. The lower extremities did not respond to noxious stimuli and remained in an extensor position, which was also slightly more pronounced on the right side. Both the upper and the lower extremities greatly resisted passive motion. The patient had no verbal responses. The eyes could not be opened with verbal or painful stimuli. Both pupils were completely dilated and not reactive to light. The eyeballs were divergent. Corneal responses were bilaterally absent.

The horizontal oculocephalic response, however, was intact, while the vertical response was minimal. Swallowing reflex was minimal but also intact. Respiratory patterns were regular. Deep tendon reflexes could not be evaluated because of the massive increased muscle tone. Plantar response was extensor, bilaterally, more prominent on the right side. Tachycardia and retention of urine were also present. Initially the patient scored four on the Glasgow coma scale.

Magnetic resonance imaging of the brain was performed to detect brainstem infarction or supratentorial mass lesions. There were no

pathological findings. Common metabolic disorders such as hypoglycaemia or hyperglycaemia, hepatic or renal failure, electrolyte disorders, disorders of systemic acid-base balance, and hyperthyroidism were excluded by laboratory examinations. Urine samples for benzodiazepines and morphines were negative. Analysis of cerebrospinal fluid to exclude subarachnoidal haemorrhage or infectious disease showed normal cell count, protein concentration, and cytology. Possible status epilepticus was also considered. However, administration of 10 mg diazepam had no effect.

The next neurological examination was performed three hours later. Vital signs were stable. The upper limbs were still in a flexor position and the lower limbs were still extensor; however, the increased muscle tone began to decrease and was less resistant to passive motion. He withdrew abnormally from painful stimuli. Plantar response was extensor on the right side. The pupils were still dilated and not reactive to light but both corneal reflexes were intact. No verbal responses could be obtained. He now scored six on the Glasgow coma scale. Seven hours later he was sitting in his bed in a state of confusion. Over the next hours, the patient's neurological signs subsided gradually.

Finally, we were informed about the intake of *D stramonium* seeds. Analysis of blood samples found increased concentrations of alkaloids. Treatment during the clinical course was supportive with cardiopulmonary monitoring. Thirty six hours after admission the patient was discharged in good clinical condition, without neurological deficits except amnesia regarding the acute toxic episode.

Coma from exogenous poisons or drugs is a common diagnostic problem, not only because of the variety of clinical symptoms but also because of incomplete medical histories and misguided efforts by families and friends to conceal facts. Even if a particular toxic agent is suspected, results of a chemical analysis may arrive too late. Therefore, an accurate and immediate diagnosis depends mostly on the clinical findings.

Our patient presented with coma in a decorticate posture. Initially a severe multifocal brainstem infarction or supratentorial mass lesions were suggested. However, the discrepancies of deep coma, absent brainstem reflexes such as corneal reflexes and non-reactive dilated pupils, and, on the other hand, the intact oculocephalic and swallowing reflex, and especially the regular respiratory patterns made the findings inconclusive and a toxicological cause probable. Moreover, vital signs were stable and magnetic resonance imaging of the brain, cerebrospinal fluid, and laboratory examinations showed no major pathological findings.

D stramonium is misused for its hallucinogenic effects. It can be obtained as a herb, as a powder, and as seeds. The typical anticholinergic effects of *D stramonium* are well known. Coma with focal neurological signs and decorticate posture is an unusual presentation of *D stramonium* intoxication. However, the presence of coma in our patient was linked to the atropine effect, described as the central anticholinergic syndrome, which has been reported in the literature.⁵

Physostigmine, which may reverse anticholinergic toxicity, was not administered because it can produce severe complications such as seizures and cardiac arrhythmia.^{1,4} Moreover, the patient's neurological symptoms subsided gradually.

Regarding this uncommon clinical presentation, the pharmacological interaction between ethanol and *D stramonium* must also be taken into account. However, as far as we are aware, no clinical or pharmacological interactions between ethanol and *D stramonium* in humans have been described in the literature.

D stramonium intoxication with the clinical picture of coma, decorticate posture, and focal neurological signs is an important clinical observation, which must be taken into account in other comatose states.

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