Increased serum concentrations of tissue plasminogen activator correlate with an adverse clinical outcome in patients with bacterial meningitis

Bacterial meningitis is the most common serious infection of the central nervous system. It is still characterised by high mortality and morbidity in adults. In this disease extensive perpetuated inflammation with leucocyte invasion into the central nervous system (CNS) results in breakdown of the blood–brain barrier and promotes neuronal damage.

Tissue type plasminogen activator (tPA) has been shown to have various biological effects that could have an impact on the pathophysiological changes observed in bacterial meningitis. In the CNS, endothelial cells, microglia, astrocytes, and neurons can produce the 70 kDa protein tPA, which normally does not cross the blood–brain barrier. Raised tPA levels in the cerebrospinal fluid (CSF) have previously been reported for certain CNS diseases such as multiple sclerosis, leukemia, and encephalitis, and raised tPA serum levels for patients with sepsis.

tPA converts plasminogen into plasmin, a rate limiting step in the proteolysis of fibrin, but also in the degradation of extracellular matrix, matrix metalloproteinase activation, and the processing of growth factors and cytokines. Further, tPA has been shown to increase neuronal cell death during excitotoxicity and cerebral ischaemia. Thus tPA may promote blood–brain barrier disruption, promote inflammatory signalling, and neuronal damage, and so be involved in the pathophysiology of bacterial meningitis.

We studied the expression of tPA in the CSF and serum of 12 patients with bacterial meningitis (causative pathogens: *St. pneumoniae* (8); *S. aureus* (3); *H. influenzae* (1)) who had been admitted to our hospital (median age 63 years; range 29 to 78). Clinical outcome was measured according to the Glasgow outcome scale (GOS; 1, death; 2, persistent vegetative state; 3, severe disability; 4, moderate disability; 5, good recovery). Ten patients with non-inflammatory neurological diseases (median age 37 years; range 23 to 81) and 10 patients with Guillain–Barré syndrome, an inflammatory demyelinating polyradiculoneuropathy in which blood–CSF barrier breakdown occurs without CSF pleocytosis, served as controls (median age 59 years; range 34 to 84).

A lumbar puncture was done and venous blood collected for diagnostic purposes after the patient’s informed consent had been obtained. CSF and serum concentrations of tPA were measured by a specific enzyme linked immunosorbent assay (TINeliz®, Biopool International, Ventura, California, USA; detection limit 1.9 ng/ml). Immunoreactive tPA concentrations are expressed as ng/ml of biological fluid.

Blood and CSF variables for the three patient groups were compared using the Mann–Whitney U test with α adjustment; a corrected p value of < 0.025 was considered significant. Bivariate correlations between clinical variables and tPA concentrations were analysed according to Spearman ρ (GOS) or Pearson (CSF leucocyte count, CSF/albumin ratio).

In all patients with bacterial meningitis, the CSF leucocyte count was markedly increased (median 1728 cells/µl; range 143 to 23.296). The CSF to serum albumin ratio (1000 × CSF albumin/serum albumin; normal < 7.4), the index used to quantify blood–CSF barrier breakdown, was significantly increased in all patients with bacterial meningitis (median 60.3; range 156 to 1400) and, to a lesser extent, in nine of the 10 patients with Guillain–Barré syndrome (median 12.8; range 4.7 to 39.0).

The tPA protein concentrations in the CSF and serum of patients with bacterial meningitis were about ninefold higher than the CSF concentrations in bacterial meningitis. In turn, the breaching of the blood–CSF barrier and an adverse clinical outcome of this disease. These findings are of particular importance in the light of earlier studies in rodent models, in which systemic infusion of tPA or plasmin resulted in blood–brain barrier disturbances in healthy control animals or in cerebral ischaemia. Disruption of the blood–brain barrier is an important pathophysiological alteration in bacterial meningitis, which contributes to CNS complications such as cerebral oedema and increased intracranial pressure. This may explain the additional correlation we found between high serum tPA levels and an adverse clinical outcome. A similar correlation was seen in patients with severe sepsis, a disease regularly associated with increased vascular permeability, in which serum tPA activity increased and was associated with mortality.

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References

Amelioration of spinal myoclonus with levetiracetam

Spinal myoclonus has been associated with various spinal cord insults, including mass lesions, ischaemia, infection, and as part of a pattern of the spinocerebellar ataxias. It has been postulated that it occurs as a result of deficient inhibitory glycinergic transmission in the spinal cord and subsequent "release" of synchronous motor neurone oscillations within segmental spinal cord circuitry, and hence a myoclonic symptom results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic symptom results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic symptom results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic symptom results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic symptom results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic symptom results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic symptom results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic symptom results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic symptom results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic symptom results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic symptom results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic symptom results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic symptom results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic symptom results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic symptom results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic symptom results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic symptom results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic symptom results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic symptom results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic symptom results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic symptom results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic symptom results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic symptom results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic symptom results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic symptom results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic symptom results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic symptom results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic symptom results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic symptom results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic symptom results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic symptom results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic symptom results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic symptom results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic symptom results in dysfunction of segmen...
Cerebral venous thrombosis (CVT) is a rare disorder, with an incidence of approximately 4–10 cases per million per year, occurring more frequently in women than in men (ratio of 4:1). CVT is a multifactorial condition, known predisposing factors include venous stasis, hypercoagulability, vasculitis, systemic lupus erythematosus, and trauma. Morality after CVT ranges from 5% to 30%. 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.

In recent years, a few thyrotoxic patients with CVT have been reported. An association between hyperthyroidism and increase of FVIII has also been described, and recent data suggest an increased incidence of venous thrombosis in patients with hyperthyroidism and level of FVIII. 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. Neurological examination was normal, except for a temporary confusional state.

A magnetic resonance venography (fig 1) revealed a 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 mU/l (reference range 0.27–4.2), free triiodothyronine of 12.1 ng/l (normal: 3.9–18.0 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’ disease. The patient was treated with thiamazole (3×10 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 A 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. 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. 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 propanolol inhibits the increase of FVIII in patients with hyperthyroidism supports this theory.

In 1995 a large study was performed on 301 case-control pairs, younger than 70 with a first episode of deep vein thrombosis. 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 a multi-variate 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. 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 thrombotic 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.

Coma with focal neurological signs caused by Datura stramonium intoxication in a young man
Intoxication with Datura stramonium, which contains a variety of tropine alkaloids, produces atropine-like effects. The seeds of D stramonium (senem stramoni) in particular contain hyoscyamine, scopolamine, and atropine. Symptoms include agitation, disorientation, hallucination, flushed skin, dilatation of...
pupils, urine retention, seizures, and respiratory depression. \textit{D\,stramonium} is voluntarily used for its hallucinogenic properties.\textsuperscript{1} Its anticholinergic compounds are likely to produce delirium and stupor but rarely cause deep coma.\textsuperscript{2}

The most 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.\textsuperscript{3} We report an unusual case of \textit{D\,stramonium} intoxication in a patient who initially presented with deep coma, focal neurological signs, and decorticate posture.

The patient was a 30-year-old man who initially presented with an 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 unresponsive 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‰.

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Our patient presented with coma 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 eyeballs 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 absent 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 hyperkalaemia 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 24 hours after admission. 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 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 after 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 \textit{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 slight left-sided weakness.

Moreover, the patient's neurological symptoms subsided gradually. Regarding this uncommon clinical presentation, the pharmacological interaction between ethanol and \textit{D\,stramonium} must also be taken into account. However, as far as we are aware, no clinical or pharmacological interactions between ethanol and \textit{D\,stramonium} in humans have been described in the literature. \textit{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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