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.1 Raised tPA levels in the cerebrospinal fluid (CSF) have previously been reported for certain CNS diseases such as multiple sclerosis, leukaemia, and encephalitis,2 and raised serum tPA levels for patients with sepsis.3

tPA convert 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.4 Further, tPA has been shown to increase neuronal cell death during excitotoxicity and cerebral ischaemia.5 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: S. 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 disable; 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 (TintElize®, 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/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 increased compared with those of control patients and patients with Guillain-Barré syndrome; in both of the latter groups, tPA concentrations in the serum were not detectable in nine of 10 patients (fig 1). The serum concentrations of tPA (mean (SD)) in patients with bacterial meningitis were about ninefold higher than the CSF concentrations (22.5 (13.8) v 2.4 (1.6) ng/ml, p < 0.05). CSF and serum concentrations in individual patients were positively correlated (r = 0.733, p < 0.01). Remarkably, high serum tPA concentrations in bacterial meningitis correlated with both an increased CSF to serum albumin ratio (r = 0.818, p < 0.01) and an unfavourable outcome according to the GOS (r = 0.72, p < 0.01). The CSF to serum albumin ratio also showed a high correlation with CSF tPA concentrations (r = 0.942, p < 0.001). For patients with bacterial meningitis no correlations were found between serum tPA and CSF leucocyte count (r = -0.319, p = 0.311), between CSF tPA and CSF leucocyte count (r = -0.070, p = 0.828), or between CSF tPA and the clinical outcome (r = -0.201, p = 0.370).

On the basis of these findings, we hypothesise that increased serum tPA contributes to breaking of the blood–brain/CSF barrier in bacterial meningitis. In turn, the breaching of the blood–CSF barrier normally keeps separate from the CNS, to enter the CSF.

Our study shows for the first time that both CSF and serum tPA are increased in bacterial meningitis. Furthermore, upregulation of serum tPA correlated positively with breakdown of the blood–CSF barrier and an adverse clinical outcome of this disease. These findings are of particular importance to 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.6 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.7 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.8

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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 syndrome. 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 segments. Levetiracetam (UCB Pharma, Smyrna, Georgia, USA) is a new antiepileptic drug that has been shown recently to reduce the effect of glycinergic inhibitors. We describe three patients whose spinal myoclonus was markedly ameliorated by levetiracetam.

Case reports

Patient 1: spinal epidural compression

A 62 year old woman with known diffuse large cell lymphoma presented to her oncologist with progressive back pain accompanied by a band-like sensation around her waist. In the preceding four weeks, she had also been treated for spontaneous involuntary abdominal contractions, and in the preceding two weeks these were accompanied by involuntary jerks of her legs. The patient could not suppress these spontaneous movements; movement of her voluntary leg movements often precipitated them, she was unable to walk safely because of numerous falls. She denied any limb weakness and bladder or bowel incontinence.

On examination, she had a mild spastic paraparesis with 4+/5 MRC grade power in a bilateral leg weakness and 3+ knee and ankle jerks, and extensor plantar responses bilaterally. There were frequent resting myoclonic jerks of her lower extremities, involving both proximal and distal musculature, occurring at a rate of 15–250/min. There were also occasional, infrequent resting myoclonic jerks affecting the trunk. The myoclonic jerks were exacerbated in amplitude during attempts to perform purposeful movements, suggesting the phenomenology of action myoclonus. The abnormal movements, rather than weakness, made it impossible for her to stand or walk unassisted. Magnetic resonance imaging (MRI) of her spinal cord revealed malignant infiltration of the lower thoracic vertebrae with evidence of cord compression at T11. An EEG was normal.

She was treated with a maximum tolerated dose of clonazepam (1 g/day) with minimal improvement. She was then started on levetiracetam 250 mg twice daily, and within three days the resting and action myoclonus subsided markedly, such that she was able to walk with assistance. On examination, the myoclonic jerk frequency in her lower extremities had decreased to 5–10/min, and the jerk amplitude was markedly diminished.

Patient 2: zoster myelitis

A 12 year old boy presented with a three month history of rhythmic spasms of his right thigh. One month before this symptom, he had had onset of bilateral leg weakness and paraesthesiae and was diagnosed as having acute transverse myelitis. The paraparesis largely resolved within two weeks of onset, but one month later he began having constant, rhythmic movements in his right quadriceps and hamstrings. These jerks could not be suppressed voluntarily and made walking difficult. Cerebrospinal fluid analysis and an MRI of the spinal cord were normal. An EEG did not show any epileptiform activity. Sodium valproate (1000 mg/d), phenytoin (300 mg/d), and intravenous lorazepam (as often as 2 mg every 4 hours) failed to relieve the constant myoclonus. A trial of 1250 mg/d of levetiracetam was used successfully to treat three patients of whom two had Unverricht–Lundborg disease and one had postmyoclonic myoclonus.

Our case, as well as the aforementioned reports of suppression of post-hypoxic and postencephalitic myoclonus with levetiracetam, suggest that this agent is promising for the treatment of both non-cortical and cortical myoclonus. These observations need to be confirmed in additional patients. Furthermore, the proportion of responders needs to be determined in a larger group of patients, ideally in the setting of a randomised, double blind, placebo controlled trial.

References

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 4/100,000 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. Maleity 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 in patients with hyperthyroidism is also described, and recent data suggest an increased incidence of venous thrombosis in patients with hyperthyroidism and high FVIII levels. 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. Electrocorticography demonstrated a slow cortical activity 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 lesion in the left temporal region. 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 offered to stop smoking. Extensive screening for coagulopathies including antiphospholipid syndrome, dysfibrinogenemia, and antiplatelet antibodies, resulting in normalisation of FVIII levels. This report emphasises 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 each 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.

References

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

Figure 1

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 stramonii) in particular contain hyoscyamine, scopolamine, and atropine. Symptoms include agitation, disorientation, hallucination, flushed skin, dilatation of...
pupils, urine retention, seizures, and respiratory depression. D stramonium is voluntarily used for its hallucinogenic properties. Its anticholinergic compounds are likely to produce delirium and stupor but rarely cause deep coma.

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. We report an unusual case of D stramonium intoxication in a patient who initially presented with deep coma, focal neurological signs, and decorticate posture.

The 30 year old 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‰. Magnetic resonance imaging of the brain, cerebrospinal fluid analysis, body temperature, and blood oxygenation, were normal. No verbal responses could be obtained. He now hypothesized 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 incomplete medical histories 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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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.

Physostigmine, which may reverse anticholinergic toxicity, was not administered because it can produce severe complications such as seizures and cardiac arrhythmia. 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.

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