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 serum tPA 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, proinflammatory 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 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 (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 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 increased compared with those of control patients and patients with Guillain-Barré syndrome; in both of the latter groups, tPA concentrations in the CSF 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) × 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 = 0.350).

On the basis of these findings, we hypothesise that increased serum tPA contributes to breaching of the blood–brain/CSF barrier in bacterial meningitis. In turn, tPA promotes blood–CSF barrier disruption, 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 usually 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 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 of the cord. 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 had been diagnosed as having thoracic herpes zoster (at T8) and had subsequent post-herpetic neuralgia. The back movements became so painful that they were interfering with her sleep. She had been told that no treatment was possible, and that the movements consisted of sudden jerks of her legs and the movements became more frequent during attempts to sit or stand. 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 pyramidial pattern in the lower extremities (quadriceps, hamstrings, and tibialis anteriores) and decreased ankle jerks, and extensor plantar responses bilaterally. There were frequent restituting myoclonic jerks of her lower extremities, involving both proximal and distal musculature, occurring at a rate of 15–20/min. There were also occasional, infrequent restituting 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 spine revealed changes consistent with segmental compression of the spinal cord at T11–T12. An EEG was normal. MRI of the thoracic spine was performed and it demonstrated increased signal intensity at the T11–T12 level consistent with an epidural compression. The patient was treated with levetiracetam (2000 mg/day) and intravenous lorazepam (as often as 2 mg a day). Five days later, the myoclonic motor activity decreased, and the patient was able to walk and stand with a walker. She was considered to be in the setting of spinal myoclonus induced by augmenting glycinergic transmission in the spinal cord and thus diminishing myoclonic focus.

In a recent open label trial of levetiracetam in eight patients with chronic myoclonus, three of five patients with chronic myoclonus experienced reduction in their myoclonus severity, as assessed by the unified myoclonus rating scale.1 The one patient in this study with spinal myoclonus showed no improvement with levetiracetam. Moreover, the time course and the average duration of symptoms in these patients was 7.6 years, ranging from one to 17 years, in contrast to our three patients whose symptoms were one to three months in duration before levetiracetam treatment. It is therefore possible that the differential responsiveness to levetiracetam was because the aforementioned non-responder had a chronic myoclonus condition whereas our responders had subacute evolving spinal cord injuries.

In a recently published study, levetiracetam was used successfully to treat three patients with posthypoxic and postencephalitic myoclonus, two of whom had failed to respond to valproic acid and clonazepam.2 Add-on therapy with levetiracetam was shown to suppress disabling post-hypoxic cortical reflex myoclonus in a 16 year old boy.3 In another study, levetiracetam was effective in the treatment of myoclonus in a patient with a previously unreported variant of the motor neurone disease, Unverricht–Lundborg disease and one patient with postanoxic myoclonus.4 In our cases, 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


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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 1/100,000 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. Majority 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 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 contraceptives 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 rhythms in the left temporal region, without epileptic activity. Brain computed tomography revealed a left temporal hypodense lesion, without iodine, without enhancement, without transformation of the associated venous sinus.

Magnetic resonance imaging revealed a left temporal hypodense lesion, without enhancement, without transformation of the associated venous sinus. 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, thrombophilia, and thrombocytopenia was negative. Further analysis revealed a state of hypercoagulability with a TSH value below 0.015 mIU/l (normal: 0.5–5.5 mIU/l), free triiodothyronine 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’ 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 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 hyperthyroidism, necessitating 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 active 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 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. 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.

References


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 (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 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 patient was a 30-year-old woman who 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 tests for electrolyte disorders, renal or hepatic failure, and hypoglycaemia or hyperglycaemia found no major pathology. Blood alcohol concentration was 1.1‰. The patient was presented in a decorticate posture. The upper limbs were in a paraplegic position with increase of flexion tonus to noxious stimuli, which was more pronounced on the right side. The lower extremities greatly resisted passive motion. The patient withdrew abnormally from painful stimuli. The eyeballs could not be opened with verbal or painful stimuli. Both pupils were completely dilated and did not react to light. The eyebrows were convergent. Corneal responses were bilaterally absent.

The horizontal oculocerebral 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 were ruled out by blood tests. Doppler ultrasound and MRI studies showed no signs of deep coma. The EEG was not diagnostic, and no seizures were detected. The patient was discharged in good clinical condition. Thirty-six hours after admission the patient was discharged.

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 patient had no verbal responses. The eyes could not be opened with verbal or painful stimuli. The eyeballs were not reactive to light. The eyeballs were dilated 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 withdrew abnormally from painful stimuli. The eyeballs could not be opened with verbal or painful stimuli. Both pupils were completely dilated and did not react to light. The eyeballs were convergent. Corneal responses were bilaterally absent.

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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. 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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Amelioration of spinal myoclonus with levetiracetam

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