LETTERS

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), which normally does not cross the blood–brain barrier, may be involved in the pathophysiology of bacterial meningitis.

We studied the expression of tPA in the CSF 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 assessed using the Glasgow outcome scale (GOSE); death; 1, severe disability; 2, moderate disability; 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 (CSF) 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 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) vs 2.4 (1.6) ng/ml; p < 0.005). CSF and serum concentrations in individual patients were positively correlated (r = 0.733, p < 0.001). Remarkably, high serum tPA concentrations in bacterial meningitis correlated with both an increased CSF to serum albumin ratio (r = 0.818, p < 0.001) and an unfavourable outcome according to the GOSE (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 an 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 = 0.530).

On the basis of these findings, we hypothesise that increased serum tPA contributes to breaching of the blood–brain barrier in bacterial meningitis. In turn, the breaching of the blood–brain/CSF barrier in bacterial meningitis, which contributes to CNS complications such as cerebral oedema and increased intracranial pressure, 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 typically 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 presented with a prolonged history of involuntary axial and pyramidal muscle contractions and voluntary leg movements. She had had progressive back pain accompanied by a band-like sensation around her waist. In the preceding four weeks, she had also been treated for various spinal and 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; moreover, 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 mild spastic paraparesis with 4+/5 MRC grade power in a pyramidal pattern in the lower extremities (quadriceps, hamstrings, and tibialis anterior), 3+ patellar fixation 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 15–25/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 a phenomenon of action myoclonus. The abnormal movements, rather than weakness, made it impossible for her to stand or walk unassisted. Magnetic resonance imaging (MRI) of the cervical spine revealed meningioma involving 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 months the resting and action myoclonus subsided markedly, such that she was able to walk safely. 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

An 83 year old woman presented with a three month history of involuntary trunk movements. The movements consisted of sudden extensor jerks of her back. They were spontaneous, occurring several times a day with no obvious provoking factors. Of note, two months before the onset of the movements, she had been diagnosed as having thoracic herpes zoster (at T8) and had subsequent post-herpetic neuralgia. The back movements began as the pain was subsiding. The movements were not painful, but were distressing to the patient as they were socially embarrassing. She was unable to suppress the movements voluntarily. She had been seen by another neurologist who had treated the movements with sodium valproate. She unfortunately received no benefit from this despite a maximum tolerated dose of 2000 mg/day. Past medical history was notable for cardiac arrhythmia and pacemaker placement.

On examination, she had brief, irregular, extensor movements of her thoracic spine, occurring every 10–30 seconds. An EEG was normal. MRI of the thoracic spine was precluded because of her pacemaker. The patient was started on levetiracetam at a dose of 250 mg twice a day. Within 24 hours of starting this treatment, the myoclonic movements completely ceased. Two months later, she began to have clusters of repetitive movements once to twice daily for periods of 20–60 minutes. Her dose of levetiracetam was increased to 500 mg twice a day. The movements again ceased, but because of sedation and dizziness at this higher dose, the dosage was halved to 1 g/day. At this dose, she was well tolerated, she has been having brief clusters of myoclonic movements two or three times a week.

Patient 3: transverse 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 proximal leg weakness and sensory loss in the lower limbs, as well as irregularity of his sleep pattern. At this time, he was treated with a maximum tolerated dose of clonazepam (1 g/day) with minimal improvement. He was then started on levetiracetam at 250 mg daily and within three months his myoclonus responded. However, 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 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 sodium valproate and clonazepam. On add-on therapy with levetiracetam was shown to suppress disabling post-hypoxic cortical reflex myoclonus in a 16 year old boy. In another study, severe action myoclonus was suppressed by levetiracetam in three patients, of whom two had Unverricht–Lundborg disease and one had postanosomous myoclonus.

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.

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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 4–10000 per year, occurring more frequently in women than in men (ratio of 1.29:1). 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 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 seizures, preceded by a short period of sweating, nausea, vomiting and photophobia. Personal and family medical histories were unremarkable. She had been taking oral contraceptives for several years and smoked two cigarettes per day. Personal and family medical histories were unremarkable. She had been taking oral contraceptives for several years and smoked two cigarettes per day. Personal and family medical histories were unremarkable.

Magnetic resonance imaging of the brain performed 24 hours later showed a non-specific enhanced 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 coagulation factors VIII and IX, was negative. Further analysis revealed a state of hyperthyroidism with a TSH value below 0.015 mIU/l (normal range 0.27–4.2), 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 activated partial thromboplastin time, while other clotting factors remain within normal limits. Moreover, correction of thyroid function results in 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.

Figure 1  Magnetic resonance venography confirms complete occlusion of the left lateral sinus.
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 second 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 30 years old and had suddenly fallen 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‰.

The patient was presented in a decorticate posture. The upper limbs were in a para- tonic flexor 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 could not be opened with verbal or painful stimuli. Both pupils were completely 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 had no verbal or painful responses. The eyeballs were divergent. Cornal 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 tonus. 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 unlikely and atropine effect, described as the central anticholinergic effect, was not administered 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 oculocerebral and swallowing reflexes, 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.

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 neurologist’s 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 comatoses states.

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