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 leukocyte invasion into the central nervous system (CNS) results in breakdown of the blood–brain barrier and promotes neuronal damage.1

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.2 Raised tPA levels in the cerebrospinal fluid (CSF) have been previously reported for certain CNS diseases such as multiple sclerosis, leukemia, and encephalitis,3 and raised serum tPA levels for patients with sepsis.4

Tissue thromboplastin initiates into plasminogen, 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.5 Further, tPA has been shown to increase neuronal cell death during excitotoxicity and cytokines.6 Moreover, tPA has been shown to activate growth factors and matrix metalloproteinase activation, but also in the degradation of extracellular matrix.7,8

Pain and the processing of growth factors are important pathophysiological alteration in bacterial meningitis, which contributes to CNS complications such as cerebral oedema and increased intracranial pressure.9 This may explain the additional correlation we found between high serum tPA levels and an adverse clinical outcome 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 the further development 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.10

On the basis of these findings, we hypothesise that increased serum tPA contributes to the breakdown of the blood–brain barrier in bacterial meningitis. In turn, the breaching of the blood–CSF barrier allows the serum tPA, which an intact 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 the further development 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.10 This may explain the additional correlation we found between high serum tPA levels and an adverse clinical outcome in bacterial meningitis. In turn, the breaching of the blood–CSF barrier allows the serum tPA, which an intact blood–CSF barrier normally keeps separate from the CNS, to enter the CSF.

In all patients with bacterial meningitis, the CSF leukocyte 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 bacterial meningitis 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) ng/ml; 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 = 0.733, p < 0.01).

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References


Figure 1 [A] Concentrations of tissue type plasminogen activator (tPA) in the cerebrospinal fluid (CSF) of control patients (controls, mean (SD)): 1.54 (0.15) ng/ml, patients with bacterial meningitis (2.42 (1.59) ng/ml), and patients with Guillain-Barré syndrome (GBS, 1.50 (0.02) ng/ml). [B] Concentrations of tPA in the serum of controls (9.71 (6.92) ng/ml), patients with bacterial meningitis (22.51 (13.84) ng/ml), and patients with GBS (13.28 (8.74) ng/ml). *p < 0.025 v control patients; †p < 0.025 v patients with GBS. Dotted line: detection limit of the assay.
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 glycineergic transmission in the spinal cord and subsequent "release" of synchronous motor neurone oscillations within segments of the spinal cord. Levetiracetam (UCB Pharma, Smyrna, Georgia, USA) is a new antiepileptic drug that has been shown recently to reduce the effect of glycineergic inhibitors. We describe three patients whose spinal myoclonus was markedly ameliorated by levetiracetam.

Case reports

Patient 1: spinal epidural compression

A 62 year old man 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 troubled by 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; 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 a mild spastic paraparesis with 4+5 MRC grade power in a pyramidal pattern in the lower extremities (quadriceps, hamstrings, and tibialis anteriors), 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 15-20 Hz. 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 phenomenonology of action myoclonus. The abnormal movements, rather than weakness, made it impossible for her to stand or walk unassisted. Magnetic resonance imaging (MRI) revealed a malignant subdural and extradural plantar responses bilaterally. There were frequent resting myoclonic jerks of her lower extremities, involving both proximal and distal musculature, occurring at a rate of 15–20 Hz. 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 phenomenonology of action myoclonus. The abnormal movements, rather than weakness, made it impossible for her to stand or walk unassisted. Magnetic resonance imaging (MRI) revealed a malignant subdural and extradural collection in 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 rest 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 paresthesiae 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 spasms of 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 intrathecal baclofen and levetiracetam was started with a good effect, but one month later he began having 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 decreased to 200 mg daily. At this well tolerated dose, 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 bilateral leg weakness and paresthesiae 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 spasms of 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 intrathecal baclofen and levetiracetam was started with a good effect, but one month later he began having 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 decreased to 200 mg daily. At this well tolerated dose, she has been having brief clusters of myoclonic movements two or three times a week.

Discussion

Glycine is a major inhibitory neurotransmitter in the spinal cord, and it has been postulated that deficient inhibitory glycineergic transmission results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic focus in the spinal cord. This postulate is based on studies of animal models of myoclonus and an in vitro model of spinal myoclonus. The latter study showed that blockade of glycine receptors in isolated spinal cord preparations from neonatal rats enhanced a central pattern generator responsible for 5 to 15 Hz synchronous motor neurone oscillations. Interestingly, these oscillations—generated from as few as two isolated segments—were synchronised over at least six spinal cord segments, suggesting extensive excitatory cortical spinal cord circuitry. Therefore, it is possible that the effectiveness of levetiracetam in our patients may be related to these glycineergic mechanisms. Levetiracetam has been shown to reverse inhibition of glycine receptors in isolated spinal cord and thus dampening down spinal glycineergic oscillations.

In a recent open labelled trial of levetiracetam in eight patients with chronic myoclonus, three of five patients with cervical myoclonus experienced reduction in their myoclonus severity, as assessed by the unified myoclonus rating scale. The one patient in this study with spinal myoclonus showed no improvement with levetiracetam. 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. It is therefore possible that the differential responsiveness to levetiracetam was because the aforementioned non-responder had a chronic fixed 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. 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 postanoxic myoclonus.

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 4.0-10.000 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. 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 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 contraceptive medication for several years and smoked two cigarettes a day. Neurological examination was normal, except for a temporary confusion state that lasted less than 24 hours. Electroencephalography demonstrated a slow rhythm 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 revealed a left temporal hypodense lesion, 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 revealed a left temporal hypodense lesion, without 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 subsequently benefits 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 (senna stramonii) in particular contain hyoscyamine, scopolamine, and atropine. Symptoms include agitation, disorientation, hallucination, flushed skin, dilatation of

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

References
pupils, urine retention, seizures, and respiratory depression. \textit{D. stramonium} is voluntarily used for its hallucinogenic properties. Its anticholinergic compounds are likely to produce delirium and stupor but rarely cause deep coma.

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. 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 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‰. 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 greatly resisted passive motion. The plantar responses were extensor. The eyeballs could not be opened with verbal or painful stimuli. Both pupils were completely dilated and not reactive to light but both corneal reflexes were intact. No verbal responses could be obtained. He now typed 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 \textit{D. stramonium} seeds. Analysis of blood samples found increased concentrations of alkaloids. Treatment during the clinical course was supportive with cardiorespiratory monitoring. Thirty-six hours after admission the patient was discharged in good clinical condition, without neurological deficits except anemia regarding the acute toxic episode.

Coma with focal neurological signs and decorticate posture is an unusual presentation of \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.

### References