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. To 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, microglial 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, leukaemia, 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, 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: Streptococcus 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 (TinTElliz; 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 a 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) vs 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 a 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 hypothesised that increased serum tPA contributes to breaching of the blood–brain/CSF barrier in bacterial meningitis. In turn, the breaching of the blood–brain/CSF barrier in bacterial meningitis, which promotes blood–CSF barrier disruption, promotes inflammatory demyelinating polyradiculoneuropathy, and so be involved in the pathophysiology of bacterial meningitis. To this end, we investigated whether serum tPA could be used to predict the clinical outcome in patients with bacterial meningitis.

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 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. Thus tPA may promote blood–brain barrier disruption, 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 primary 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 segmental motor neurones. 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 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; merely 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). She had bilateral ankle jerks, and extensor planter 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 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) of her spinal cord demonstrated abnormal T2-hyperintense signal in the posterior columns of her spinal cord. The magnetic resonance imaging (MRI) of her brain was normal. An EEG showed rhythmic repetitive waves at 30 Hz bilaterally, consistent with a myoclonic status. Cerebrospinal fluid analysis and an MRI of her sella were normal.

A trial of intravenous lorazepam (as often as 2 mg times a week) and of intravenous diazepam helped to reduce her myoclonus slightly. A trial of botulinum toxin A injections into the right quadriceps did not reduce the myoclonus. A trial of clonazepam 250 mg twice daily, and within three months of starting this treatment, the myoclonic movements completely ceased. Two months later, she began to have clusters of repetitive movements once or 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 then reduced to 250 mg/day. At this lower dose, well tolerated, she has been having brief clusters of myoclonic movements for two to three times a week.

Patient 2: zoster myelitis

An 85 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 pace-maker 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 able to walk 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 or 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 dosages was then reduced to 250 mg/day. At this lower well tolerated dose, she has been having brief clusters of myoclonic movements for two to 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 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 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 intramuscular botulinum toxin A injections into the right quadriceps did not ameliorate the movements.

On examination, he had constant, semi-rhythmic myoclonus of his right quadriceps at 120–150 beats per minute, with his knee extended, and of his right hamstrings with his knee flexed. The myoclonus was not suppressed by patellar fixation, but did improve slightly with concentration on mental tasks. On power testing, there was 4+/5 MRC grade power in the right quadriceps and right hamstrings. A repeat EEG was again unremarkable. He was started on levetiracetam at 250 mg daily and the dose increased over a four week period to 1250 mg/d. No clinical change was noted until the 1250 mg dose was reached, at which point the myoclonus slowed and then completely ceased. Two months later, she had also been started on levetiracetam and within three months of starting this treatment, the myoclonic movements again ceased, but because of sedation and dizziness at this higher dose, the dosage was then reduced to 250 mg/day.

Discussion

Glycine is a major inhibitory neurotransmitter in the spinal cord, and it has been postulated that deficient inhibitory glycine transmission results in dysfunction of segmental spinal circuitry, and hence a myoclonic focus in the spinal cord. This postulate is based on studies of animal models of myoclonus and in vitro studies 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 commissural projections. However, 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 and GABA currents induced by negative allosteric modulators, such as zinc and β-carbolines.

It may therefore conceivably be of benefit in patients with spinal myoclonus by augmenting glycineergic transmission in the spinal cord and thus dampening down myoclonic focality. In a recent open labelled trial of levetiracetam in eight patients with chronic myoclonus, three of five patients with corticospinal 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 treatment. 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 a subacute evolving spinal cord injury.

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, therapy with levetiracetam was shown to suppress disabling post-hypoxic cortical reflex myoclonus in a 16 year old boy. In another study, therapy with levetiracetam was shown to suppress disabling post-hypoxic cortical reflex myoclonus in a 16 year old boy.

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.

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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 4–10000 per year, occurring more frequently in women than in men (ratio of 4/1). 1, 11 CT and MRI scans often reveal absence of the associated venous infarct. 1

In recent years, a few thyrotoxic patients with CVT have been reported. 1, 5 An association between hyperthyroidism and increase of FVIII has also been described, 6 and recent data suggest an increased incidence of venous thrombosis in patients with hyperthyroidism and high FVIII levels. 5 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 confusion, preceded by a short period of perspiration, verbal agressiveness, and disorientation. Four days before admission, she had developed a sudden, pulsatile 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, and hyperhomocystaemia, 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 analyses revealed a state of hyperthyroidism with a TSH value below 0.015 mU/l (normal: 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-Basedow’s 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 lithium. 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. 5 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. 5 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.
A 30 year old male patient was admitted to Kaiser Franz Josef Hospital, Kundratstrasse 3, 1100 Vienna, Austria, after suffering a head 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 para tonic 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 caloric reaction was absent. 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 oculocerephalic response, however, was intact, while the vertical response was minimal. Swallowing reflex was preserved 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 hypocalcaemia 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 one and a half hours after the sudden onset of symptoms. There was no evidence of trauma. Vital signs, such as cardiological 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 diagnosis of 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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