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 neurones 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.

Tissue plasminogen activator (tPA) increases neuronal cell death during excitotoxicity and cerebral ischaemia. Thus tPA may 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: 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).

Increased tPA correlates with raised serum tPA levels in bacterial meningitis

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) v 2.4 (1.6) ng/ml; p < 0.005). 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 breaching of the blood–brain/CSF barrier in bacterial meningitis. In turn, increased tPA serum concentrations may contribute to the increased systemic blood–CSF barrier permeability that occurs in this disease.

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.

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F Winkler, S Kastenbauer, U Koedel, H W Pfister

Department of Neurology, Klinikum Grosshadern, Ludwig-Maximilians University Munich, Marchioninistr. 15, D-81377 Munich, Germany

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Correspondence to: Dr H W Pfister; pfister@nerv.med.uni-muenchen.de

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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 paraneoplastic syndrome.1 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.2 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

An 82 year old woman presented 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 continuous involuntary abdomino-lumbar 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, involuntary 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 manner (quadriceps, hamstrings, and tibialis anterior), 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 15–25 Hz per second. 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 the cervical spine revealed a large mass effect on the spinal cord at T11. An EEG was normal.

She was treated with a maximum tolerated dose of clonazepam (1 g/d) with minimal improvement. She was then started on levetiracetam 250 mg twice daily, and within 24 hours her movements ameliorated. 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 reduced to 500 mg/day. At this dose she was well tolerated, she has been having brief clusters of myoclonic movements two or 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 to three 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 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 again reduced to 500 mg/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 bilateral leg weakness and sensory neuropathy in his right lower limb. He was diagnosed as having acute transverse myelitis and was discharged as having acute transverse myelitis.

The paraparesis largely resolved within two weeks of onset, but one month later he began having constant, rhythmic jerks 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 show a focal 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. At a trial dosage of 1000 mg/day of levetiracetam, the myoclonus was markedly ameliorated. 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 stopped over a seven day period, allowing independent ambulation. Other than mild initial sedation, no side effects were experienced.

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 circuitry, and hence a myoclonic condition results from a reduction in the spinal cord. This postulate is supported by studies of animal models of myoclonus3 and an in vitro model of spinal myoclonus.4 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 connections.

It is possible that the effectiveness of levetiracetam in our patients may be related to these glycineergic mechanisms. Levetiracetam has been shown to reverse glycineergic transmission in the spinal cord and thus dampening down myoclonic focci.

In a recent open labelled 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.5 The one patient in this study with spinal myoclonus showed no improvement with levetiracetam. However, in 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 was started. 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.6 Add-on therapy with levetiracetam was shown to suppress disabling post-hypoxic cortical reflex myoclonus in a 16 year old boy.7 In another study, he had bilateral leg weakness and was suppressed by levetiracetam in three patients, of whom two had Unverricht–Lundborg disease and one had postanoxic myoclonus.8

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 will 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.

C Keswani, E H Kossoff, G L Krauss

Department of Neurology, The Johns Hopkins University, 600 North Wolfe Street, Baltimore, Maryland 21287, USA

C Hagerty

Neurology Specialists, Columbia, Maryland, USA

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Correspondence to: Dr G L Krauss; gkrauss@jhmi.edu

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 4–10,000 per year, occurring more frequently in women than in men (ratio of 1:2.9). 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 CVT 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 medicine, which contains a variety of tropine alkaloids, prompting 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, hyperhomocysteinemia, 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 analysis revealed a state of hyperthyroidism 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 (3x10 mg/day), followed by the administration of radioactive iodine (9 mCi). One month after discontinuation of thyroidal contraceptives, thyroid tests remained increased. FVIII procoagulant protein showed a marked increase: 1680 IU/l (normal limits: 500–1500 IU/l) and remained slightly raised five weeks later. Meanwhile the patient developed a hypothyroidism, necessitating a substitution 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 the 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 a 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 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 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. \textit{D} \textit{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} \textit{stramonium} intoxication in a patient who initially presented with deep coma, focal neurological signs, and decorticate posture. The 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 cardipulmonary 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 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 pupils were regular. Deep tendon reflexes 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 scored 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} \textit{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 with focal neurological signs and decorticate posture is a common diagnostic problem, not only 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 oculocephalic and swallowing reflex, and especially the regular respiratory pattern 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.

\textit{D} \textit{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 \textit{D} \textit{stramonium} are well known. Coma with focal neurological signs and decorticate posture is an unusual presentation of \textit{D} \textit{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 \textit{D} \textit{stramonium} must also be taken into account. However, as far as we are aware, no clinical or pharmacological interactions between ethanol and \textit{D} \textit{stramonium} in humans have been described in the literature. \textit{D} \textit{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.

S Oberndorfer, W Grisold
Department Neurology and LBI for Neurooncology, Kaiser Franz Josef Hospital, Kundratstrasse 3, 1100 Vienna, Austria

G Hinterholzer, M Rosner
Intensive Care Unit, Kaiser Franz Josef Hospital, Kundratstrasse 3, 1100 Vienna, Austria

Competing interests: none declared
Correspondence to: Dr S Oberndorfer; stefan.oberndorfer@kfkj.mw.gv.at

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