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) 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, leukaemia, and encephalitis, and increased serum tPA levels for patients with sepsis.

The CSF tPA converts plasminogen into plasmin, a protein which breaks down fibrin and promotes blood–brain barrier disruption, thereby allowing 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 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. Disruption of the blood–brain barrier is 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


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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 spontaneous 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 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 woman presented with diffuse large cell lymphoma occurring two hours after a band-like sensation around her waist. In the preceding four weeks, she had also been seen by a non-invasive 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; made voluntary leg movements after 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 anterior) at rest and ankle jerks, and clonus and 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, suggestive of the phenomenon 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 large epidural lesion in the thoracic spine. Physical examination demonstrated involvement of 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 resting and action myoclonus subsided markedly, such that she was able to walk. On examination, the myoclonic jerk frequency in her lower extremities had decreased to 5-10/min, and the jerk amplitude was markedly diminished.

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 oscillation 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 collaterals. Theorists conclude that it is possible that the effectiveness of levetiracetam in our patients may be related to these glycineergic mechanisms. Levetiracetam inhibits the glycine-gated chloride channel by augmenting glycineergic transmission in the spinal cord and thus dampening down myoclonic firing.

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-responders 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. 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.

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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 4–10,000 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. 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 perseverance, 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 pills 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 showed a slow arythmia 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, showed a non-specific hyperintense 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 and deficiencies in antithrombin, protein C and S, hyperhomocysteinaemia, 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 <0.05 mIU/L), free triiodothyronine of 12.1 ng/ml (normal: 9.3–18.0 ng/ml), and an increased free thyroxin of 28.8 ng/ml (normal: 9.3–18.0 ng/ml). Anti-TSH receptor antibodies were found consistent with Graves-Basedow’s disease. The patient was treated with thiamazole (3x10 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: 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 active period of 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 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 (sermen 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.

A 30 year old male patient was admitted to Kaiser Franz Josef Hospital, Kundratstrasse 3, 1100 Vienna, Austria, Intensive Care Unit, Kaiser Franz Josef Hospital, Kundratstrasse 3, 1100 Vienna, Austria, Department Neurology and LBI for Neurooncology, Kaiser Franz Josef Hospital, Kundratstrasse 3, 1100 Vienna, Austria. Correspondence to: Dr S Oberndorfer; stefan.oberndorfer@kfj.mwien.gv.at

Our patient presented with coma in a decorticate posture. Initially a severe multifocal neurological signs were stable. The upper limbs were still in a flexor position and the lower limbs were still extensor; however, the increased muscle tone began to decrease and was less resistant to passive motion. He withdrew abnormally from painful stimuli. Plantar response was extensor on the right side. The pupils were still dilated and not reactive to light but both corneal reflexes were intact. No verbal responses could be obtained. He now hypotonia 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 D stramonium seeds. Analysis of blood samples found increased concentrations of alkaloids. Treatment during the clinical course was supportive with continuous cardiac monitor- ing. Thirty six hours after admission the patient was discharged in good clinical condition, without neurological deficits except amnesia regarding the acute toxic episode.

Coma from exogenous poisons or drugs 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 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 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.

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Coma with focal neurological signs caused by *Datura stramonium* intoxication in a young man

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