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 extravasate to the CSF. In bacterial meningitis, the blood–brain barrier is disrupted and the CSF contains increased levels of tPA. Enlarged venules and small arteries in patients with bacterial meningitis were found to express increased tPA activity.

Increased serum concentrations of tPA correlated with the clinical outcome of bacterial meningitis. Patients with high serum tPA concentrations had a poorer clinical outcome than those with low tPA concentrations.

The correlation between serum tPA concentrations and clinical outcome suggests that tPA might be a biomarker for predicting the outcome of bacterial meningitis. Further studies are needed to confirm these findings and to investigate the mechanisms underlying the association between serum tPA concentrations and clinical outcome.

References


Competing interests: none declared.
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 synchronou r motor neurone oscillations within segments of the cord. Levetiracetam (UCB Pharma, Smyrna, Georgia, USA) is a new antiepileptic drug that has been shown to block the glycinergic spinal cord circuitry, and hence a myoclonic oscillation results in dysfunction of segmental spinal motor neurones. It may therefore conceivably be of benefit in patients with spinal myoclonus by augmenting glycinergic 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 posthypoxic 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 amelioration with levetiracetam. How ever, 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 long-standing 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 patient with postanoxic myoclonus, who was not significantly improved by levetiracetam, 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 the 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 treated with 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 reduced to 250 mg/day. At this well tolerated dose, she has been having brief clusters of myoclonic movements two or three times a week.

Case reports
Patient 1: spinal epidural compression
A 62 year old man was 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 involuntary involuntary abdominal contractions, and in the preceding two weeks these were accompanied by involuntary jerks of her leg. The patient could not suppress these spontaneous movements; nor were voluntary leg movements often precipitated. 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 (quadriiceps, 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 130–150/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 phenomenology 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 cervical spine revealed malignant infiltration 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 unassisted. 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 factor. Of note, two months before the onset of the movements, she had been diagnosed as having thoracic herpes zoster (at T8) and had subsequent postherpetic 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 the 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 treated with 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 reduced to 250 mg/day. 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 glycinergic 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 neuron 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 control.

It is possible that the effectiveness of levetiracetam in our patients may be related to these glycinergic mechanisms. Levetiracetam is a non-competitive negative allosteric modulator of glycine receptors, shown to enhance glycinergic transmission in vivo. How ever, 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 glycinergic transmission in the spinal cord and thus dampening down myoclonic focci.

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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 4/1 000 000 per year, occurring more frequently in women than in men (ratio of 4/1).1 CVT is a multifactorial condition, known predisposing factors include venous stasis, hypercoagulability, vasculitis, systemic lupus erythematosus, and trauma. Mortality after CVT ranges from 5% to 30%.1 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.2

In recent years, a few thyrotoxic patients with CVT have been reported. An association between hyperthyroidism and increase of FVIII has also been described,3 and recent data suggest an increased incidence of venous thrombosis in patients with hyperthyroidism and high FVIII levels.4 Here we report a patient with increased FVIII levels and an autoimmunthyroidism, 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 perspiration, 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 confusional state that lasted less than 24 hours. Electroencephalography demonstrated a slow arrhythmia 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, dysfunction 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 range: 0.35–4.5 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 recep
tor 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: 500–1500 IU/l), and remained slightly raised five weeks later. Meanwhile the patient had developed a hypothyroidism, necessitating the resection of the thyroid gland.

Discussion

Increase of clotting FVIII occurs in several conditions such as strenuous exercise, fever, pregnancy, renal failure, adrenaline (epine
phrine) infusion, nephrotic syndrome, 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.6 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.7 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 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.8 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 tropane alkaloids, produces atropine-like effects. The seeds of D stramonium (samen stranoni) 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.

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 D stramonium intoxication in a patient who initially presented with deep coma, focal neurological signs, and decorticating posture.

A 30-year-old 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 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%. He was presented 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 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 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 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, hypoglycaemia 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 five hours later. Vital 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 was in a deep coma 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 cerebral pressure 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 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 between coma, absent brainstem reflexes, and non-reactive dilated pupils, and, on the other hand, the intact oculocerebral and swallowing reflexes, 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 decorticating 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.

Coma with focal neurological signs and decorticating posture, and focal neurological symptoms is an important clinical observation, which must be taken into account in other comatose states.

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References
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