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 raised serum tPA levels for patients with sepsis.

Tissue-type plasminogen activator (tPA) converts plasminogen into plasmin, a protease that breaks down fibrin and plasminogen activator can function as a cofactor for the breakdown of the blood–brain barrier in bacterial meningitis. In turn, the breaching of the blood–brain/CSF barrier in meningitis 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 in 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
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. It has been postulated that it occurs as a result of deficient inhibitory glycnergic transmission in the spinal cord and that it is reversible. The latter study showed that spinal myoclonus is ameliorated by augmenting glycnergic transmission in the spinal cord and thus dampening down myoclonic focis.

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. 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. Therefore, it is possible that the differential response 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, amelioration of myoclonus experienced reduction in their myoclonus severity, as assessed by the unified myoclonus rating scale.


discussion

glycnergic transmission in the spinal cord, and it has been postulated that deficient inhibitory glycnergic transmission results in dysfunction of segmental spinal motor neurone oscillations within segmental spinal cord segments. 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 connectivity. It is possible that the effectiveness of levetiracetam in our patients may be related to these glycnergic mechanisms. Levetiracetam has been shown to reverse the depression of glycine and GABA gated 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 glycnergic transmission in the spinal cord and thus damping down myoclonic focis.

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 4/1,000,000 per year, occurring more frequently in women than in men (ratio 1:2.9). CVT is a multifactorial condition, known predisposing factors include venous stasis, hypercoagulability, vasculitis, systemic lupus erythematosus, and trauma. Malignancy 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 per- system dimensions: 612.0x792.0

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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, and coma. The treatment of choice is atropine injection, which should be given slowly to avoid excessive atropine levels.
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 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%.

Neurologically, he 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. There was no plantar response. The eye 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 oculofacial response, however, was intact, while the vertical response was minimal. Swallowing reflex was present 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 hyperkalemia or hyperglycaemia, hepatic or renal failure, electrolyte disorders, disorders of systemic acid-base balance, and hyperthermia 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 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 D 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 an unusual presentation of D stramonium poisoning. Importance of 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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