Letters

The cytopathogenic agent in CSF: evidence for a relationship with enolase levels

Sir: We have previously described a cytopathic effect induced *in vitro* by some cerebrospinal fluid (CSF) samples[1] which has been observed with CSF from patients with a variety of neurological and psychiatric conditions.[2] Despite early suggestions that a virus-like agent may have been involved in the production of the cytopathic effect we later demonstrated that the effect could be observed in the prescence of inhibitors of protein synthesis. This was inconsistent with the effect being due to an active viral infection.[3] Recently Mered *et al*[4] reported a failure to detect any evidence for viruses present in the CSF of schizophrenics. Although their negative virological findings do not necessarily conflict with our results we were surprised at their failure to report the development of a cytopathic effect in any of their tests.

A coded series of 91 CSF samples was retested according to the method described previously.[3] In spite of a storage time of up to five years in some cases, 72 of the samples gave identical results, a concordance ($p < 0.001$) which shows that we are dealing with a reproducible phenomenon. In a recent report[5] the retesting of 53 CSFs in a different laboratory also produced a highly significant relationship between the initial findings and the retest ($p < 0.01$).

As the cytopathic effect was noted in CSFs from a wide variety of neuropsychiatric and degenerative conditions, including schizophrenia, dementia and Huntington's chorea, we were interested in the question of what could be common to these conditions. As cellular degeneration is either known or has been postulated to occur in all of these conditions, we measured enolase levels as a general marker of pathological change in the CNS which could be measured in CSF. Levels of enolase enzymes are elevated in cases of human herpes encephalitis, Huntington's chorea[6] and anoxic conditions of the CNS.[7] The increase in enolase levels has been attributed to the leakage of proteins due to cell damage,[8] alpha enolase being released by non-neuronal (including glial) cells and gamma enolase being a neuronal specific isoenzyme.

We measured both alpha and gamma enolase levels by radioimmunoassay[6] in a coded series of CSF samples from psychiatric patients diagnosed as either schizophrenic or affective, and compared cytopathic effect-positive samples with cytopathic effect-negatives using Student's *t* test. A significant ($p < 0.02$) relationship was observed between cytopathic effect status and increased alpha enolase concentrations. The increase in gamma enolase levels observed in the cytopathic effect-positives was not significant (table).

We conclude that, although the cause has not yet been identified, the cytopathic effect is a reproducible phenomenon, and is associated with elevated CSF alpha enolase levels. This may reflect cell damage in the CNS or blood brain barrier of some psychiatric patients, although it remains to be determined whether the *in vitro* cytopathogenic component is a cause or a product of such damage.

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Table *Enolase (ng/ml) in CSF*

Cytopathic effect	*Present*	*Absent*	
Alpha enolase (SEM)	13·9 (1·3)	10·1 (0·9)	$p < 0.02$
Gamma enolase (SEM)	15·1 (1·4)	12·0 (0·8)	$p < 0.07$
N	11	23	
Mean age (yr)	27·6	33·9	
Age range (yr)	25–59	18–60	

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Computed tomography and acute carbon monoxide poisoning

Sir: According to Sawada *et al*,[1] low-density areas in the globus pallidus in CT scans soon after severe carbon monoxide poisoning suggest a poor outcome. A close correlation between such CT scans and pathological findings has been established.[2] However, such low-density lesions may appear later involving different pathological mechanisms and with a different prognosis, as shown in the case reported below.

A 22-year-old Caucasian woman presented in Rabat on 25 November 1981 after carbon monoxide poisoning. The initial coma lasted at least four hours. She left the hospital the day after. On 1 December 1981, headache and visual disturbance appeared with distortion of optical images and micropsia. She was transferred to Lille. The patient was aggressive. There was diffuse hypotonia with brisk tendon reflexes in the lower limbs; the plantar responses were flexor. The EEG showed 5 Hz slow waves anteriorly and 2 Hz slow waves in the parietal areas bilaterally. CT scan was normal. Her symptoms disappeared within 72 hours, but there was bradyphrenia and the EEG remained abnormal. A new CT

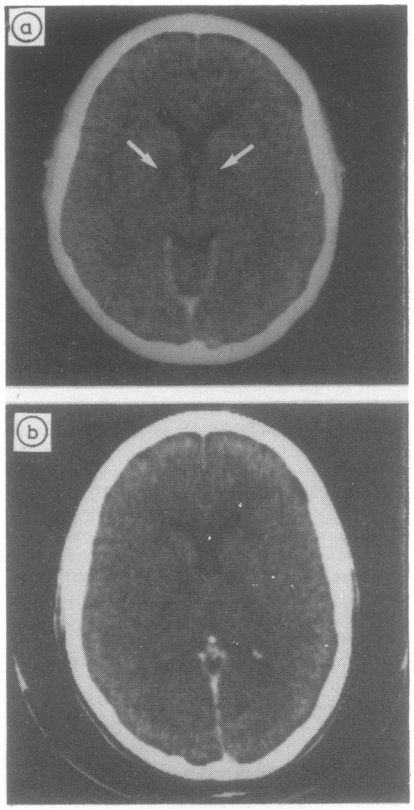

Fig *CT scans with contrast enhancement: (a) 26 days (b) 13 months after acute carbon monoxide poisoning. Arrow indicates bilateral areas of low-density in the globus pallidus.*

scan, 26 days after carbon monoxide poisoning, revealed marked low-density areas in the globus pallidus (fig a). Over the next week, the patient became very apathic and remained so for ten days. The relatives noticed obsessional behaviour concerning her clothing which lasted for one month. The EEG returned to normal. A year later, she was normal and the CT scan was normal (fig b).

In the cases of severe carbon monoxide poisoning presented by Sawada *et al*,[1] low-density areas suggesting selective degeneration of the globus pallidus were observed on CT scans performed a few hours after injury. Nardizzi has described a later appearance (8th day) of CT scan changes in the globus pallidus consisting in an abnormal enhancement with contrast medium.[3] Our case emphasises that globus pallidus low-density areas can also appear late after carbon monoxide poisoning (in our case 26 days). The early and the late CT scan lesions originate from different processes. The early lesion may be due to glial alterations similar to those found in the globus pallidus by Foncin in 1978[4] after carbon monoxide poisoning. Hypodense lesions in the globus pallidus, which in our case disappeared a year later, accompanied by behavioural changes, have also been described by Laplane[5] in a case of bilateral pallido-striatal necrosis due to encephalopathy after a wasp sting.

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Isoniazid and action tremor in multiple sclerosis

Sir: Isoniazid has been reported to help the action tremor of patients with multiple sclerosis.[1] We used isoniazid to treat five consecutive patients with this problem and followed the patients up for eighteen months.

All patients had clinically definite multiple sclerosis.[2] They all had a tremor of both arms which although inconspicuous at rest was very marked on assuming a posture. It often spread to involve the whole body. Where the finger-nose test was possible there was no increase in tremor at the extremes of movement. The patients were all wheelchair bound, mainly because of the tremor, and the functional ability of their arms was measured by recording their ability to feed, wash and dress themselves. The tremor was assessed by four simple bedside tests: drawing a straight line between two crosses, measuring the amount of water spilt from a glass held in the outstretched hand, building a tower of three bricks, and assembling nine boxes of descending size inside one another. Between five and ten days practice was given before starting isoniazid, 300 mg daily in divided doses. The daily dose was increased by 300 mg every three days up to 1200 mg daily or the occurrence of side effects.

Pyridoxine 150 mg daily was given concurrently. Acetylator status was measured before starting treatment[3] and liver function tests were performed at weekly intervals during it.

The tremor improved in four of the five patients while on isoniazid. Functionally, two found it easier to walk with a Zimmer aid and two others propelled their wheelchairs more easily (see table). Three patients gained the ability to drink from a cup and two the ability to feed themselves. All four patients showed an improvement in two or more of the functional tests. The patients who improved did so within three days of starting treatment and if the drug was discontinued they reverted to their previous state in a similar time period. The remaining patient showed no improvement over a two week period and the drug was then discontinued.

All four patients who improved developed weakness of the lower limbs of upper motor neuron distribution. In one, who was on carbamazepine for a seizure disorder, this was associated with extensor plantars, marked drowsiness, and elevation of aspartate transaminase and alanine transaminase to four times normal. When the dose of isoniazid was reduced and the anticonvulsant changed to primidone these symptoms and signs disappeared and the tremor remained controlled. The other patients who were weak complained of mild drowsiness. Reducing the dose of isoniazid abolished the weakness and drowsiness but still controlled the tremor. Aspartate transaminase and alanine transaminase were increased to twice normal in