LETTERS TO THE EDITOR

Acute dystonia due to clozapine

Since the introduction of antipsychotic drugs in the early 1950s the term "neuroleptic" implied the closely connected antipsychotic drug effects and neurological side effects on the motor system. Soon after its introduction, clozapine demonstrated its clinical efficacy in the treatment of schizophrenic psychoses. Extrapyramidal side effects have rarely been noted and clozapine has been called an "atypical neuroleptic".

We report an unusual case of acute dystonia in a 50-year-old male schizophrenic patient. He was first treated in 1977 with haloperidol, in 1985 the medication was switched to clozapine because of marked extrapyramidal side effects under haloperidol. Further exacerbations followed each time that clozapine was increased from the maintenance dose of 100 mg to up to 600 mg/daily. In 1990 the patient was again admitted to hospital with paranoid-ideation, psychomotor agitation and aggression. Under a dose of 400 mg clozapine the symptoms slowly abated over a time of five weeks, while diazepam 5 mg twice daily was given, tapered and discontinued. In the sixth week of treatment two days after the discontinuation of diazepam the patient suffered from an acute dystonic syndrome with retrocollic torsion and dystonic cramps of the tongue and mouth. The clozapine dose had remained unchanged at 400 mg/daily. The acute dystonia was successfully treated with intravenous biperiden 5 mg. Despite oral administration of an anticholinergic drug (biperiden 4 mg/daily) the acute dystonia recurred after four days and had to be treated again with intravenous biperiden. After an increased dose of biperiden (4 mg twice a day) no recurrence of the acute dystonia was noted. After tapering the clozapine dose to 250 mg the anticholinergic was discontinued without further recurrence of dystonic incidents.

The ECG, EEG, chest *x*-ray, CT of the brain and routine blood chemistry including TPHA and thyroid function did not reveal any abnormalities. At the time of the acute dystonia the clozapine serum level was 1·1 mg/l (reference 0·2–0·7 mg/l). The serum drug screening and the test for phenothiazines and butyrophenones was negative.

This extrapyramidal syndrome was a classic acute dystonia which has not been reported with clozapine. Such a syndrome may be considered more typical in a younger male patient, but several aspects are remarkable and atypical. Acute dystonias usually appear 12–72 hours after first administration of the neuroleptic. Our patient had been treated for weeks with the same dose of clozapine, which had led to a relatively high clozapine level in the serum, the only change in medication being the discontinuation of a benzodiazepine. The possibility of accidental or conscious ingestion of typical neuroleptics was excluded by blood-testing for phenothiazines and butyrophenones. The appearance of an acute dystonia after such a long time of treatment and unchanged dose would lead us to the conclusion, that the rare incidence of EPS with clozapine is not due, as proposed earlier, to its weak D2-receptor blockade and relatively marked antimuscarine (anticholinergic) properties alone. The dopamine/acetylcholine model of dyskinetic side effects under neuroleptics oversimplifies the pathophysiology of the basal ganglia. Combined chlorpromazine with an anticholinergic (benzatropine) caused more EPS than clozapine mono-treatment.[1] Although the exact mechanism of action of clozapine is uncertain, more complex mechanisms like the high D1-receptor blockade of clozapine[2] or the marked antiserotonergic properties[3 4] must be involved. Some authors speculate on the action of clozapine on the gabaergic system, which has been implicated in the pathogenesis of dyskinetic reactions.[5] In our case a benzodiazepine—which exerts its action at GABA-receptors—had been stopped shortly before the acute dystonia.

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Changes in CSF amino acid concentrations during the evolution of amyotrophic lateral sclerosis

There is increasing evidence that neuroexcitatory mechansims may be involved in the pathophysiology of amyotrophic lateral sclerosis (ALS). Glutamate, a neuroexcitatory transmitter, has specific neurotoxic effects. High glutamate levels have been observed in the plasma of fasting patients with ALS and the presence of a systemic glutamate metabolism defect[1] or an abnormal distribution between the neurotransmitter and metabolic glutamate pools have been suggested to occur in ALS. Moreover, glutamate and aspartate depletion were reported to occur in the spinal cord and brain in patients with ALS.[2] The plasmatic levels may, however, have reflected the neurotransmitter concentrations in the non-neuronal tissues of ALS patients, and necropsied tissues have shown biochemical changes characteristic only of the end-stages of the disease. Several authors therefore measured amino acids in the CSF of patients with ALS.[3 4] Here we compared 1) the amino acid concentrations in the CSF of 10 ALS patients at the time of diagnosis with those of control subjects with neurological disorders; 2) the concentrations in the same patients at the time of diagnosis with those measured one year later.

Ten patients with ALS, six women and four men, aged 52–85 years (mean 62·9) were examined by two or more experienced neurologists, and all met the Escurial diagnostic criteria. No history of heavy metal intoxication, monoclonal gammapathy, antibodies against gangliosides or endocrine abnormalities were noted. Routine CSF analyses were normal. No patient took branched chain amino acids. The duration of the symptoms at the time of CSF sampling ranged from five to 36 months (mean: 13). The severity of the disorder[3] was rated using a numerical disability index from 1 to 4. In the ALS patients, the severity ranged from 1 to 4 (mean 2·7). All except one of the patients were ambulatory and all had a normal food intake. In 5 of the 10 patients with ALS, CSF was also obtained on the twelfth month following the first sample. The severity indexes were 3 or 4 (mean 3·6).

The control group consisted of 10 patients, five women and five men, aged 44–82 (mean 56·3), who had a variety of neurological disorders other than neurodegenerative diseases. The severity of the illness (4-point scale) ranged from 1 to 4 (mean 2·6). Informed consent was obtained from both the patients with ALS and the control subjects.

The same aliquots of CSF were obtained by lumbar puncture after an overnight fast and were collected on ice and frozen immediately at −80°C until analysed. The amino acid levels were measured in a blind fashion in parallel in the same assay using an HPLC method coupled with fluorometric detection of the compounds after deproteinization with perchloric acid and precolumn derivatization with o-phthalyl dialdehyde.

In agreement with the results of a previous study,[3] our data showed that no significant changes occurred in the CSF glutamate concentrations of our ALS patients (table 1) compared with control subjects, whereas other authors have reported increases in the levels of these amino acids.[4] No significant correlations were found to exist between the glutamate level versus age, CSF protein concentration, severity or duration of the disease. Aspartic acid was either undetectable or present only

Table 1 Mean (SD) CSF aminoacid concentrations in neurological controls and patients with ALS at diagnosis (μmol/l)

	Neurological controls	*Patients with ALS*
Aspartic acid	0-trace	0-trace
Asparagine	4·8 (1·0)	5·3 (1·9)
Glutamic acid	0·9 (0·3)	0·9 (0·2)
Serine	12·1 (2·4)	11·8 (4·3)
Glutamine	339 (59)	294 (59)
Taurine	4·5 (1·4)	4·3 (1·2)
Alanine	12·9 (3·4)	13·9 (6·7)
Tryptophan	0·8 (0·7)	0·6 (0·3)
Valine	11·2 (4·3)	11·8 (5·3)
Phenylalanine	8·0 (1·9)	8·5 (3·3)
Isoleucine	3·2 (0·7)	3·6 (1·3)
Leucine	8·9 (3·0)	8·8 (4·0)

Table 2 Mean (SD) CSF aminoacid concentrations in five patients with ALS at diagnosis and one year later (μmol/l)

	Time of diagnosis	One year later
Aspartic acid	0-trace	0-trace
Asparagine	5·0 (1·3)	9·6 (1·1)**
Glutamic acid	0·8 (0·3)	0·8 (0·3)
Serine	10·7 (3·6)	14·5 (2·1)
Glutamine	289 (29)	257 (30)
Taurine	3·4 (0·8)	4·2 (0·8)
Alanine	19·9 (2·1)	23·5 (4·6)
Tryptophan	0·4 (0·2)	1·3 (0·3)**
Valine	9·6 (3·6)	23·5 (4·6)**
Phenylalanine	8·5 (2·4)	17·4 (3·1)**
Isoleucine	3·9 (1·2)	7·3 (1·4)*
Leucine	10·5 (3·7)	17·9 (3·8)*

*p < 0·05, **p < 0·01 according to the Mann-Whitney U test.

in trace amounts in the CSF of the patients.

One year after the diagnosis of the disease, an increase was observed in the asparagine, isoleucine, leucine, phenylalanine and tryptophan CSF concentrations (table 2). The mean valine concentration decreased. Aspartic acid and glutamic acid levels were not affected. These results fit previous data showing that an increase occurred in the phenylalanine, isoleucine, leucine, valine, isoleucine, leucine, and tryptophan CSF levels of ALS patients.[3] Unlike these authors, however, we did not observe any significant differences in the lysine, alanine,[3 4] arginine, glutamine[3] or serine[4] levels.

These results might be mainly attributable to a general deterioration in the patients' condition, decreased activity, or abnormalities in their nutritional status. A general deterioration of the metabolic status may also have been responsible. Although none of our patients had any biological marks of hepatic failure, ultrastructural abnormalities of ALS patients' hepatocytes have been reported[5] and hepatic failure may be correlated with an increase in brain phenylalanine, tryosine and tryptophan.

Several factors have been suggested to account for the discrepancies between the published data: the total glutamate and asparate concentrations measured in the control subjects differ tremendously between Perry's[3] and Rothstein's[4] studies. Using the HPLC technique our results with the neurological controls were of the same order of magnitude as those reported on healthy volunteers by other authors.

We did not observe any significant changes in the CSF glutamate or asparate levels in our patients who had been symptomatic for 13 months at the time of diagnosis and for 25 months at the time of the second CSF analysis. Furthermore, like Perry,[3] we did not observe any significant correlations between the CSF glutamate levels and age. This may suggest that the neuroexcitatory toxic mechanism, if it occurs, mostly takes place early in the course of the disease, probably before the onset of clinical ALS, and that the discrepancies between studies on the CSF glutamate levels may not be attributable only to the progression of the disease in the patients tested.

At the end-stage of the disease, the anterior horn motor neurons degenerate and the spinal glutamate concentration decreases.[2] This decrease is usually correlated with the loss of glutamatergic nerve terminals. The loss of glutamatergic afferents might be due to an excess of glutamate, and glutamatergic neurons might become irreversibly damaged before the onset of clinical ALS. Due to the decreased tissue glutamate levels, one might have expected to observe a decrease in the CSF glutamate level. Since the glutamate CSF level remained normal[3] or became elevated in some patients that had been symptomatic for 15 months,[4] glutamate turnover may increase in the surviving neurons.

We thank Professor J Pouget and Professor C Desnuelle who kindly referred several patients with ALS. We are grateful to the patients with ALS who provided CSF specimens. The English revision was carried out by Dr J Blanc.

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Selective enhancement of executive function by idazoxan in a patient with dementia of the frontal lobe type

The coeruleocortical noradrenergic system has long been implicated in the process of focused attention and more recently in controlled or effortful processes, and the allocation of attention.[1] Broadly speaking the prefrontal cortex seems to be essential for tasks that require directed attention and effortful processing—tasks such as reasoning, anticipation, goal establishment, planning, organisation of behaviour, and monitoring of feedback. These terms are often subsumed under the heading "executive function". Psychopharmacological studies in experimental primates and humans have implicated the noradrenergic system as an important modulator of frontal lobe function.[2 3 4] These behavioural observations are supported by neuroanatomical ones, as there is a high density of noradrenergic α_2 receptors in the frontal cortex.[5] Two recent reports have suggested that it may be possible to improve performance on tests of frontal function using noradrenergic drugs such as the mixed α_1/α_2 adrenoceptor agonist clonidine, and the more selective α_2 adrenoceptor antagonist idazoxan.[3 4]

We report enhancement of executive function by idazoxan in a male patient with mild dementia of the frontal lobe type. A consultant neurologist (JRH) made a diagnosis of frontal type dementia, supported by the result of his SPECT scan, which showed right frontal hypometabolism. On neuropsychological assessment, he was found to have a relatively specific pattern of frontal dysfunction. For example, his score on the mini mental state examination was normal (29/30) whereas his score on verbal fluency was severely impaired compared with that of normal volunteers, and comparable with that of neurosurgical patients with frontal lobe excisions. A 40 mg oral dose of idazoxan was given to the patient on two occasions with a double-blind, placebo-controlled protocol. Test sessions were separated by at least a 40 hour washout period, and an ABBA design was used so as to counterbalance any order effect. A range of computerised tests measuring attention, memory, and planning was given, in an attempt to pinpoint a selective effect of idazoxan on tests with a large executive component, implicating the frontal lobes. This dose was well tolerated and except for transient nausea and a slight increase in blood pressure (25/15 mmHg), no adverse reactions occurred.

A selective improvement was found. Specifically, idazoxan improved the efficiency of planning by reducing the number of excess moves made on the Tower of London test of planning (figure). Furthermore, idazoxan increased the patient's verbal fluency for categories and also the percentage of correct detections made on a rapid visual information processing (RVIP) test of sustained attention. The Tower of London and verbal fluency have been shown to be sensitive to frontal lobe dysfunction, and current investigations in our own laboratory suggest RVIP is another such test. By contrast, no change in performance was found for tests of paired associates learning, pattern and spatial recognition, or digit span. Such a selective pattern of cognitive enhancement supports

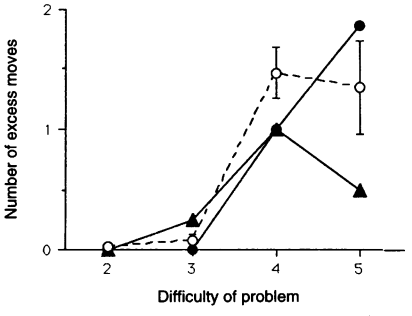

Figure Beneficial effect of idazoxan (▲) compared with placebo (●) on problem-solving performance in the Tower of London test of planning, in a patient with dementia of the frontal lobe type. Performance is measured as the number of excess moves required to solve the problem; the lower the excess moves, the better the performance. Difficulty of problem refers to whether a problem requires a minimum of 2,3,4, or 5 moves for completion. The control data (○) were obtained from a sample of volunteers (n = 12) matched to the patient for age, sex and estimated premorbid IQ. Bar = SE.