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 neuroleptic 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". A remarkable 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 effects under haloperi- dol. 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, tapering and discontinued. In the sixth week of treatment two days after the discontinuation of diazepam the patient suf- fered from an acute dystonic syndrome with retrocolic 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 continuation of an anticholinergic drug (biperiden 4 mg/daily) the acute dysto- nia 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 dys- tonic was noted. After tapering the clozap- ine dose to 250 mg the anticholinergic was discontinued without further recurrence of dystonic incidents.

The EEG, 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 dysto- nia 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 discontinu- ation of a benzodiazepine. The possi- bility of accidental or conscious ingestion of typical neuroleptics was excluded by blood-testing for phenothiazines and butyro- phenones. 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 to its proposed earlier, to its weak D2-receptor blockade and relatively marked antimuscarine (anti- cholinergic) properties alone. The dopamine/acetylcholine model of dyskinetic side effects under neuroleptics oversimpli- fies the pathophysiology of the basal gan- glia. Combined chlorpromazine with an anticholinergic (benzatropine) caused more EPS than clozapine mono-treatment. Although the exact mechanism of action of clozapine is uncertain, more complex mech- anisms like the high D1-receptor blockade of clozapine5 or the marked antiserotonergic properties6 must be involved. Some authors speculate on the actions of clozapine on the gabaergic system, which has been implicated in the pathogenesis of dyskinetic reactions.7 In our case a benzodiazepine— which exerts actions on GABA-recep- tors—had been stopped shortly before the acute dystonia.

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2 Faede L, Acar M, Cerletti AL, Seddah G. D1- and D2-dopamine receptor occupa-
4 Frieden RL, Sanders-Bush E, Barrett RL. Clozapine blocks disruptive stimulatory stimula-
5 Meltzer H. Clinical studies on the mech-


Changes in CSF amino acid concentra-
tions during the evolution of amy- trophic lateral sclerosis

There is increasing evidence that neuroexci-
toratory mechanisms may be involved in the pathophysiology of amyotrophic lateral scle-
rosis (ALS). Glutamate, a neuroexcitory transmitter, has shown strong neurotoxic effects. High glutamate levels have been observed in the plasma of fasting patients with ALS and the presence of a systemic glutamate metabolism defect8 or an abnormal distribu-
tion between the neurotransmitter and 


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<th>Table 1 Mean (SD) CSF aminoacid concentrations in neurological controls and patients with ALS at diagnosis (µmol/l)</th>
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<tr>
<td><strong>Neurological controls</strong></td>
</tr>
<tr>
<td><strong>Aromatic acid</strong></td>
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<tr>
<td>Aspartic acid</td>
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<tr>
<td>Glutamic acid</td>
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<tr>
<td>Serine</td>
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<td>Glutamine</td>
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<td>Asparagine</td>
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<td>Alanine</td>
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<td>Aspartic acid</td>
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<td>Glutamine</td>
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<td>Asparagine</td>
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<td>Alanine</td>
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References:
2. Frieden RL, Sanders-Bush E, Barrett RL. Clozapine blocks disruptive stimulatory stimula-
3. Meltzer H. Clinical studies on the mech-


on the symptoms at the time of CSF sampling ranged from 5 to 36 months (mean: 13). The severity of the disorder 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 obtained on the CSF-tenth 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 neuro-
degenerative diseases. The severity of the illness (4-point scale) ranged from 1 to 4 (mean 2-6). Important content 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 imme-
diately 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 perchorlic acid and precolumn derivatization with p-phthialid diahydride.

In agreement with the results of a previous study, our data showed no significant changes occurred in the CSF glutamate concentrations of our ALS patients (table 1) compared with control subjects, whereas other authors have reported

differences in the levels of these amino acids.8 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
Aspartic acid 50
Glutamic acid 1
Phenylalanine 8
Isoleucine 3
Valine 1
Taurine 2
Alanine 1
Tryptophan 0.4
Valine 1.5
Phenylalanine 5
iso-Isoleucine 3.9
Leucine 10.5

*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, iso-Isoleucine, 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, iso-Isoleucine, leucine, valine, iso-Isoleucine, leucine, and tryptophan CSF levels of ALS patients.1 Unlike these authors, however, we did not observe any significant differences in the lysine, alanine,4 arginine, glutamine1 or serine6 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 markers of hepatic failure, ultrastructural abnormalities of ALS patients' hepatocytes have been reported7 and hepatic failure may be correlated with an increase in brain phenylalanine and tryptophan.

Several factors have been suggested to account for the discrepancies between the published data: the total glutamate and asparagine concentrations measured in the control subjects differ tremendously between Perry's8 and Rothstein's9 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 asparagine 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,1 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.

Moreover, like Perry, we did not observe any significant correlations between the CSF glutamate levels and age.

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At the end-stage of the disease, the anterior horn motor neurons degenerate and the spinal glutamate concentration decreases.1 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 a decrease in the CSF glutamate level. Since the glutamate CSF level remained normal1 or became elevated in some patients that had been symptomatic for 15 months,1 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.12,13 These behavioural observations are supported by neuroanatomical ones, as there is a high density of noradrenergic α2 receptors in the frontal cortex.14 Two recent reports have suggested that it may be possible to use psychopharmacological tests of frontal function using noradrenergic drugs such as the mixed a1/α2 adrenoceptor agonist clonidine, and the more selective α2 adrenoceptor antagonist idazoxan.14

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 the 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 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 dosage 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 (RVP) 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 RVP is another such test. By contrast, no change in performance tests found in a sample of paired associated learning, pattern and spatial recognition, or digit span. Such a selective pattern of cognitive enhancement supports the idea of a selective enhancement of executive function by idazoxan in a patient with dementia of the frontal lobe type.

<table>
<thead>
<tr>
<th>Number of moves</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<tr>
<td>Difficulty of problem</td>
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<td>2</td>
<td>3</td>
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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 the problem is more difficult (1, 2, 3, 4, 5) or easier (2, 3, 4, 5) for completion. The control data (○) were obtained from a sample of volunteers (n = 12) matched to the patient for age and estimated premorbid IQ. Bar = SE.