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 antimuscarinic (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 (benzotropine) 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 clozapine² 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 mechanisms 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 defect¹ 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 Escorial diagnostic criteria. No history of heavy metal intoxication, monoclonal gammopathy, 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 disorder³ 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 amino acid 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)