Eur Arch Psychiatry Clin Neurosci (1991) 240:370–372

European Archives of Psychiatry and Clinical Neuroscience

Short Communication

Myoclonic Epileptic Seizures During Clozapine Treatment: a Report of Three Cases

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Received January 17, 1991

Summary. Three adult schizophrenic patients without a previous history of epilepsy are reported who, during clozapine treatment, developed paroxysmal EEG patterns and generalized myoclonic jerks without alteration of consciousness. These seizures were phenomenologically identical to those occurring in juvenile myoclonic epilepsy and were classified as generalized epileptic seizures. We tentatively conclude that generalized myoclonic epileptic seizures may be induced by clozapine.

Key words: Clozapine – Juvenile myoclonic epilepsy – Myoclonic seizures

Introduction

Clozapine is an "atypical" neuroleptic with powerful antipsychotic action and almost no extrapyramidal side-effects. In contrast to typical neuroleptics clozapine has a low affinity to postsynaptic D2 receptors and acts as a 5HT2 and D1 receptor blocker [5, 8, 10, 12]. Clozapine dose-dependently induces paroxysmal EEG patterns more frequently than other antipsychotics [6, 7, 11, 13]. However, it is a matter of controversy whether clozapine induces epileptic seizures more frequently than typical neuroleptics. In retrospective studies the incidence of grand mal during clozapine treatment was reported to be between 0% and 4.1% [3, 4, 5, 8, 12]. The present paper describes three patients suffering from schizophrenia who, under clozapine treatment, developed generalized myoclonic jerks which were considered to be epileptic in nature.

Case reports

Case 1. A 38-year-old man with chronic schizophrenia, paranoid type (DSM III-R 295.34), was hospitalized owing to exacerbation of the disease. There was no previous history or family history of epilepsy and no sign of organic brain disease [EEG (Fig. 1a), CT, laboratory examinations]. Owing to lack of efficacy of standard neuroleptics the treatment was changed to clozapine, beginning with 50 mg/day and reaching a maximal dose of 300 mg/day within 4 weeks. Concomitantly, the patient received 100 mg chlorprothixene. The clinical improvement was moderate. Three days after the maximal daily dose had been reached the patient experienced a sudden brief "shock-like" flexion of the knees, resulting in a fall. There was no nausea and no alteration of consciousness and the patient was able to get up immediately. Blood pressure and heart rate were normal. Two days later the patient complained about frequent brief jerks of his hands, resulting in him dropping objects. The EEG showed paroxysmal patterns (Fig. 1b). After descontinuation of chlorprothixene and dose reduction of clozapine to 200 mg/day no more seizures occurred. Another EEG 7 days later showed a trend towards normalization, but paroxysmal patterns were still present (Fig. 1c). Clozapine was discontinued.

Case 2. A 20-year-old man with schizophrenia, disorganized type (DSM III-R 295.11), was hospitalized owing to therapy resistance to neuroleptics (perazine, haloperidol). There was no previous history or family history of epilepsy and no sign of organic brain disease (EEG, CT, CSF, laboratory examinations). He was successfully treated with clozapine, beginning with 50 mg/day and reaching the maximal dose of 450 mg/day within 48 days. On the 48th day the patient twice experienced a sudden flexion of the knees and fell down, but was able to stand up immediately. In the following 2 days he repeatedly complained about sudden involuntary contractions of the shoulder and arm muscles, resulting in him throwing objects. On the 3rd day the patient again experienced a sudden massive contraction of the leg muscles and the trunk, throwing him down. There was no aura prior to and no nausea or alteration of consciousness during these episodes. An EEG recording showed paroxysmal

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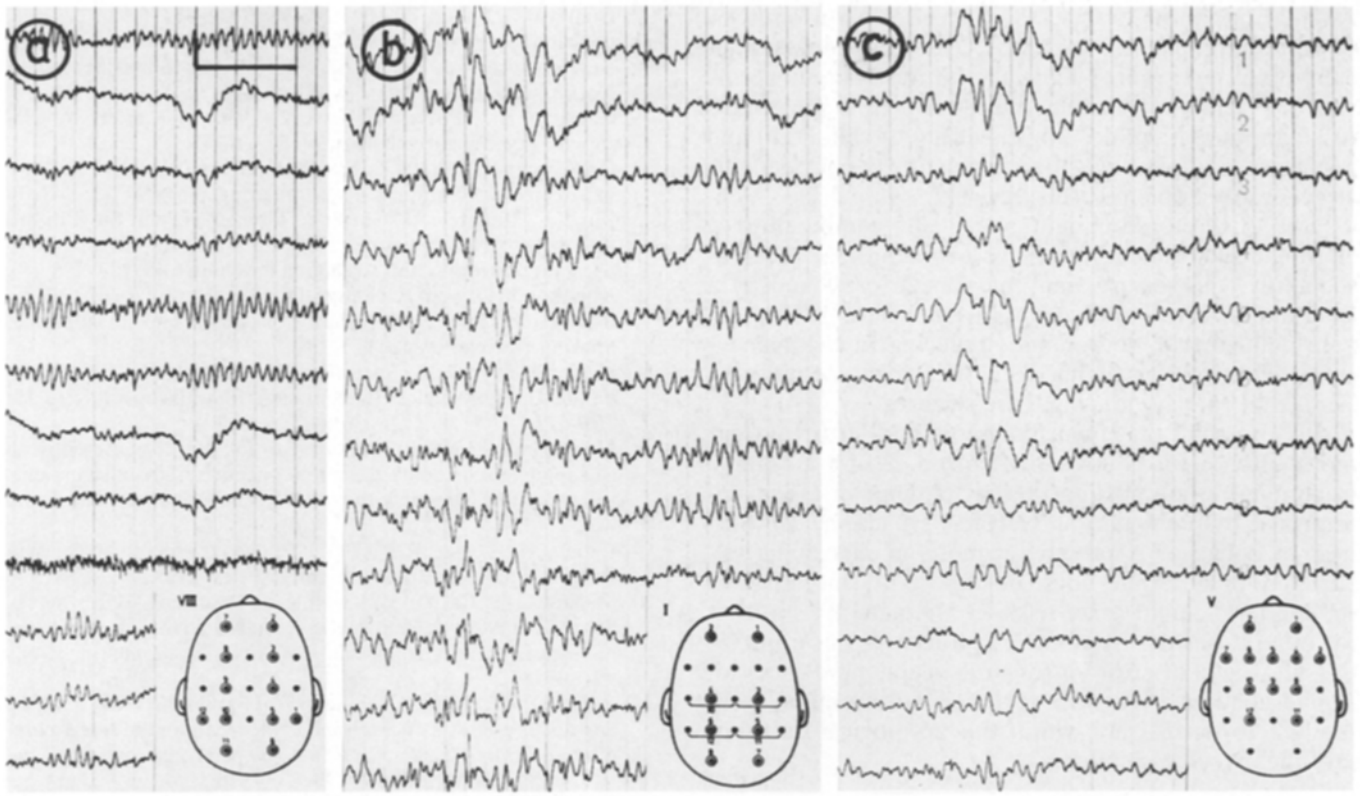

Fig. 1a–c. Case 1, EEG recordings, calibration: 50 μV, 1 s. **a** On admission (chlorprothixene 50 mg, pimozide 2 mg); **b** 33rd day of treatment (clozapine 300 mg, chlorprothixene 100 mg); **c** 40th day of treatment (clozapine 200 mg)

patterns. After adding carbamazepine to the medication, EEG recordings showed reduction of paroxysmal patterns. Three days after starting with carbamazepine repetitive weak myoclonic jerks of the hands occurred for 20–30 s. For another 2 weeks the patient repeatedly complained about a non-visible "internal tremor" of his hands, which ceased after reduction of the clozapine dose to 200 mg. The patient was maintained on combined pharmacotherapy with 200 mg/day clozapine and 450 mg/day carbamazepine. Inspite of the theoretically possible addition of haematological side-effects of the two drugs, we gave carbamazepine because of its otherwise good tolerance compared with other anticonvulsants. Haematological examinations were performed regularly and showed no abnormality.

Case 3. A 23-year-old man with schizophrenia, disorganized type (DSM III-R 295.1), with no previous history but positive family history of epilepsy was hospitalized owing to exacerbation of the disease. One year before, an EEG recording had shown one brief generalized paroxysmal pattern, but two subsequent EEGs had been normal. All other standard examinations (CT, CSF, laboratory) had shown normal findings. In the past the patient had responded to standard neuroleptics, but had developed disabling extrapyramidal side-effects. On the present admission the patient was treated with clozapine, beginning with 50 mg/day and reaching a maximal dose of 300 mg/day within 14 days. Concomitantly, he received levomepromazine. EEG recordings again showed paroxysmal activity. On the 7th day of treatment the patient experienced a sudden brief massive contraction of the leg and trunk muscles and fell down without losing consciousness or feeling dizzy. He was able to stand up immediately. Blood pressure and heart rate were normal. Levomepromazine was discontinued and diazepam (15 mg/day) was added to the medication. Another EEG recording showed only a slight reduction of paroxysmal patterns. Clozapine was discontinued and the patient was treated with a standard neuroleptic. No more seizures occurred.

Discussion

Generalized epileptic myoclonic seizures occur in some well-defined, age-related epileptic syndromes of childhood and early adulthood [9]. On the other hand, there are some forms of non-epileptic myoclonus such as "surprise" or "startle" myoclonus [1].

Our three patients had no previous history of epilepsy. Only the third patient might have had a low threshold for seizure, indicated by the positive family history and one epileptiform EEG. Clozapine induced paroxysmal generalized EEG patterns in all three patients. At clozapine doses higher than 250 mg daily the patients developed myoclonic jerks without associated alteration of consciousness and without any aura. The jerks affected the arms, legs or the whole body and showed a marked variety in intensity. There was no suggestion of cardio-

vascular origin, of "startle" or "surprise" myoclonus, or of other non-epileptic myoclonic jerks. Phenomenologically these jerks were identical with the seizures occurring in juvenile myoclonic epilepsy, which is considered to be an idiopathic, nosological entity of childhood and adolescence [2]. We classified the seizures of our patients as generalized epileptic seizures [1].

Two of the three patients received a combination of clozapine and chlorprothixene or levomepromazine. Consequently, the seizures may have been provoked by a drug interaction. However, we are not aware of any report about other neuroleptics inducing myoclonic seizures. Therefore, it seems likely that clozapine played a significant role in inducing these seizures.

It is possible that myoclonic epileptic seizures occur more often than at present realized during clozapine treatment but are not reported by patients or are misinterpreted by physicians as "surprise" reaction, nervousness or collapse. A proper diagnosis of myoclonic seizures under clozapine would be important, since massive sudden jerks might carry risks for the patient as well as for others. Besides its clinical significance, our observation may be of interest for research in epilepsy, since clozapine appears to be able to mimic seizures that were thought to occur only within the nosological entity of juvenile myoclonic epilepsy.

References

1. Commision on Classification and Terminology of the International League Against Epilepsy (1981) Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia 22:489–501
2. Dinner D-S, Lüders H, Morris H-H, Lesser R-P (1987) Juvenile myoclonic epilepsy. In: Lüders H, Lesser R-P (eds) Epilepsy: electroclinical syndomes. Springer, Berlin Heidelberg New York,pp 131–149
3. Gaertner H-J, Fischer E, Hoss J (1989) Side effects of clozapine. Psychopharmacology 99:S97–S100
4. Grohmann R, Rüther E, Sassim N, Schmidt L-G (1989) Adverse effects of clozapine. Psychopharmacology 99:S101–S104
5. Kane J, Honigfeld G, Singer J, Meltzer H, and the Clozaril Collaborative Study Group (1988) Clozapine for the treatment-resistant schizophrenic. Arch Gen Psychiatry 45:789–796
6. Koukkou M, Angst J, Zimmer D (1979) Paroxysmal EEG activity and psychopathology during the treatment with clozapine. Pharmacopsychiatry 12:173–183
7. Kugler J, Lorenzi E, Spatz R, Zimmermann H (1979) Drug-induced paroxysmal EEG-activities. Pharmacopsychiatry 12: 165–172
8. Lindström L-H (1988) The effect of long-term treatment with clozapine in schizophrenia: a retrospective study in 96 patients treated with clozapine for up to 13 years. Acta Psychiatr Scand 77:524–529
9. Lüders H, Lesser R-P (1987) Epilepsy: electroclinical syndromes. Springer, Berlin Heidelberg New York
10. Meltzer H-Y, Bastani B, Kwon K-Y, Ramirez L-F, Burnett S, Sharpe J (1989) A retrospective study of clozapine in treatment-resistent schizophrenic patients. Psychopharmacology 99:S68–S72
11. Naber D, Leppig M, Grohmann R, Hippius H (1989) Efficacy and adverse effects of clozapine in the treatment of schizophrenia and tardive dyskinesia – a retrospective study of 387 patients. Psychopharmacology 99:S73–S76
12. Povlsen U-J, Noring U, Fog R, Gerlach J (1985) Tolerability and therapeutic effect of clozapine. Acta Psychiatr Scand 71:176–185
13. Spatz R, Lorenzi E, Kugler J, Rüther E (1978) Häufigkeit und Form von EEG-Anomalien bei Clozapintherapie. Drug Res 28:1499–1500