Clozapine-induced concordant agranulocytosis in monozygotic twins

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Received 30 March 2000; revised 19 August 2000, accepted for publication 23 August 2000

Two monozygotic twin sisters were admitted to a psychiatric hospital and diagnosed as having first-episode schizophrenia. Clozapine treatment led to the complete remission of psychotic symptoms within a short time. In both twins the low leukocyte count was detected after 9 weeks of clozapine. Serological typing of the HLA system was performed and an identical pattern was detected in both twins: HLA-A: 28, 26; HLA-B: 49, 63; DR: 2 (vs 16), 12, 52; DQ:1. It is the first report of concordant manifestation of clozapine-induced agranulocytosis in monozygotic twins. Our case report of twins afflicted synchronously with schizophrenia and later with agranulocytosis after clozapine is of interest because it suggests that genetic factors may participate not only in timing of onset of schizophrenia, but also in the emergence and timing of agranulocytosis in response to clozapine treatment. (*Int J Psych Clin Pract* 2001; **5**: 71–73)

Keywords
clozapine *agranulocytosis*
monozygotic twins *genetic factors*
timing

INTRODUCTION

Clozapine was introduced into the pharmacological treatment of schizophrenia in 1972. It would have been a success, but reports in the mid-seventies on agranulocytosis in patients treated with clozapine led to a widespread restraint in its use.[1] At present the risk of agranulocytosis is estimated between 0.8 and 1%. The condition is fatal in 3–4% of those afflicted.[2,3] The search for predictors of risk for developing agranulocytosis on clozapine has so far been inconclusive. However, the existence of assumed genetic markers of clozapine-induced agranulocytosis[4] is supported by our clinical experience with the almost synchronous manifestation of schizophrenia and complications of treatment in young female monozygotic twins. They were both treated by clozapine in the early stages of the disorder and both developed clozapine-induced agranulocytosis.

CASE REPORT

Two sisters, monozygotic twins, 18 years old, developed psychotic symptoms with delusions and hallucinations. They were admitted to a psychiatric hospital and diagnosed as having first-episode schizophrenia; first, twin A and 2 weeks later, twin B.

The twins were born by Caesarean section in the eighth month of pregnancy. Both suffered perinatal asphyxia and had to be resuscitated after birth. Twin A had been treated for atopic eczema and allergic rhinitis as a child, and twin B was treated for viral meningitis at the age of 5. They had no other previous health problems and no history of psychiatric problems or counselling

After admission, twin A was treated with haloperidol, 8 mg, for 9 days. Because of prominent extrapyramidal symptoms that did not recede after adjunctive anticholinergic treatment (biperiden 6 mg p.d.), the pharmacological treatment was switched to 400 mg/day of sulpiride and adjunctive medication with clonazepam 6 mg/day. Her condition deteriorated further and after 15 days electroconvulsive treatment (ECT) was started. She received a total of 4 ECTs at intervals of 2 days. Her white blood count (WBC) was monitored regularly at weekly intervals from the beginning of clozapine treatment.

She was discharged from the hospital and referred to an outpatient unit, fully remitted, on 150 mg of clozapine per day, 6 weeks after the start of clozapine treatment, and 10 weeks after she was first admitted. Because of poor sleep, in addition to clozapine she was taking 0.5 mg of clonazepam in the evening; because of a bacterial urocystitis she also took cotrimoxazol 960 mg b.i.d. for 1 week on the recommendation of an internist. At discharge, her

leukocyte count was 13 700/ml and she had 11 260 neutrophils/ml. On her regular weekly visit to the outpatient clinic, 10 weeks after the beginning of clozapine treatment, her leukocyte count was 1400/ml. Although clozapine was immediately discontinued, the next day the patient was feverish and laboratory tests showed 1100 leukocytes/ml. She was admitted to the haematology department of a large Prague hospital, where staphylococcus pneumonia and a septic state were diagnosed. She was treated with granulocyte-stimulating growth factor (G-CSF), antibiotics (vancocin, meropene, pefloxacin) and antimycotics (fluconazol, ketoconazol). Her clinical condition was soon under control, septic signs gradually disappeared and leukocyte levels normalized after a transitory leukaemoid reaction within the next 3 weeks. However, her psychotic symptoms recurred, including additional delusional and catatonic symptoms. She did not respond to 3 weeks of treatment with the benzamide antipsychotic tiapride (400 mg p.d.). Complete remission was then reached within a week after switching to risperidone 5 mg p.d.

Twin B was admitted 2 weeks after her sister. Because it had already been established that her twin sister responded poorly to commonly used antipsychotics, she was immediately started on clozapine and her dose gradually increased to 300 mg/day. Prominent and poorly responding psychotic symptoms caused her to be given a series of eight electroconvulsive treatments during the second and the third week of her hospital stay. She was discharged free of symptoms after 8 weeks of inpatient treatment. Her blood count at discharge was 6100 leukocytes/ml and 4360 neutrophils/ml. At her regular visit to the outpatient clinic, 9 weeks after the beginning of clozapine treatment, the WBC was 1800 leukocytes/ml. Clozapine was discontinued immediately and the patient was readmitted to the psychiatric hospital unit, because a relapse of schizophrenia followed the discontinuation. The low leukocyte count persisted: after 11 weeks from the start of clozapine, it was 1900 leukocytes/ml and 4110 neutrophils/ml. After control of her psychotic symptoms was re-established, twin B was observed in the same haematological department as her twin sister. Fortunately, there were no complications, and within a week the WBC became normal, with leukocytes at 7500/ml and neutrophils 4110/ml. However, her paranoid delusions and other psychotic symptoms responded poorly to risperidone in spite of an increase in the dose to 9 mg/day. Only after another series of electroconvulsive treatments (10 treatments over 18 days) and a combined pharmacological treatment of 4 mg/day risperidone and 15 mg/day of the benzodiazepine oxazepam did her psychotic symptoms disappear completely .

In the course of the treatment, serological typing of the HLA system was performed and an identical pattern was detected in both twins: HLA-A: 28, 26; HLA-B: 49, 63; DR:2 (vs 16), 12, 52; DQ: 1.

DISCUSSION

To our knowledge, there is no report of concordant manifestation of clozapine-induced agranulocytosis in monozygotic twins. The reason may be that clozapine is not usually considered an appropriate pharmacological treatment in the first episode of schizophrenia and is probably avoided in young women, who are also known to be susceptible to haematological complications of clozapine treatment.[3] In the cases we report the decision was taken after some deliberation, because the initial poor response and prominent extrapyramidal side-effects after standard pharmacological treatment in the severely psychotic twin A. Clozapine treatment for twin B seemed to have been justified by the initial good response of her twin sister A, whose agranulocytosis manifested later, when twin B had already been admitted and started treatment.

However, our case report of twins afflicted synchronously with schizophrenia and later with agranulocytosis after clozapine is of interest because it suggests that genetic factors may participate not only in timing of onset of schizophrenia, but also in the emergence and timing of agranulocytosis in response to clozapine treatment. In both twins the low leukocyte count was detected after 9 weeks of clozapine. The diagnoses of schizophrenia were based on ICD-10 criteria, and the possibility of an induced psychotic state in one of the twins was excluded. The HLA typing provided evidence for the presence of DR2, DQ1 haplotype in our twins. It was also detected in all four affected non-Jewish patients in the report of Lieberman et al[4] on the association of a particular HLA haplotype and agranulocytosis in a population of Jewish Ashkenazi patients. This haplotype was also present in 30% of an ethnically matched population, and its role as a specific marker of vulnerability to clozapine-induced agranulocytosis requires further investigation.

KEY POINTS

- This is a description of the concordant manifestation of clozapine-induced agranulocytosis in monozygotic twins
- In both twins the agranulocytosis was detected after 9 weeks of clozapine treatment
- The case report suggests that the genetic factors may not only participate in timing of onset of schizophrenia but also in the emergence and timing of agranulocytosis in response to clozapine treatment
- Serological typing of the HLA system should be a marker of vulnerability to clozapine-induced agranulocytosis

CONCLUSION

Our report provides arguments for further enquiry into the genetic determinants of side-effect induction and response to clozapine.

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