Selective Immunoglobulin M Deficiency Among Clozapine-Treated Patients: A Nested Case-Control Study

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ABSTRACT

Objective: To analyze the presence of selective immunoglobulin M immunodeficiency (SIgMD) among long-term clozapine-treated outpatients in a nested case-control study.

Method: We investigated 33 patients who took clozapine and found 6 patients with SIgMD. These patients were compared with 67 patients not taking clozapine, of whom 2 had SIgMD. Of these 6 and 2 patients, we made a group of 8 case-patients with SIgMD. This group was compared with 92 (27 + 65) patients without SIgMD matched to cases on age, sex, weight, mental health unit, diagnosis, and psychiatric medication. In both groups there were patients who had taken clozapine: 6 of 8 in the SIgMD group (75%) and 27 of 92 in the non–SIgMD group (29%). SIgMD was defined by mean IgM values ≤ 30 mg/dL. IgM measurements were performed every 6 months, and the data were averaged for each subject. The study was conducted from January 2009 to December 2013.

Results: We found a statistical association between clozapine use and the presence of SIgMD (OR = 7.2222; 95% CI, 1.3704–38.0623; Z = 2.332; *P* = .0197).

Conclusions: Due to the high incidence of SIgMD observed in schizophrenic patients treated with clozapine, clinicians should pay particular attention to not only granulocyte counts but also patterns of IgM decline to prevent drug iatrogenesis.

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Clinicians are often encouraged to conduct studies that provide insight into the pathogenesis, diagnosis, prognosis, and treatment of different subsets of patients with schizophrenia and patients with psychotic disorders. Due to possible immunosuppressive action that may contribute to the antipsychotic efficacy, pharmacologic studies may need to extend beyond neurotransmitter activity.[1]

Clozapine is an atypical antipsychotic medication that possesses immunomodulatory properties and is indicated for patients who fail standard antipsychotic treatment. In fact, clozapine has been reported to mediate several effects on humoral immunity, such as altering the levels of antibody-producing cytokines, and has been speculated to possess immunosuppressant activity as a part of its antipsychotic properties.[2]

Selective immunoglobulin M immunodeficiency (SIgMD) is a rare form of dysgammaglobulinemia, which is characterized by a selective low level of IgM in conjunction with normal T cell numbers and function and no other identifiable immunodeficiency. SIgMD can occur as either a primary or secondary condition and has an estimated prevalence of 0.03%–3%.[3] As a secondary condition, SIgMD can be associated with immunosuppressive treatments,[4] including clozapine.

Therefore, due to speculated immunosuppressive effects of clozapine as a part of its antipsychotic effect, which can alter levels of immunoglobulins and eventually may lead to SIgMD, we investigated the presence of SIgMD among clozapine-treated patients with the purpose of clinical management.

METHOD

We conducted a case-control study nested within a cohort that included all psychiatric outpatients referred to our mental health unit in Zaragoza, Spain. The study was conducted from January 2009 to December 2013. SIgMD was defined by mean IgM values ≤ 30 mg/dL during the 5-year follow-up period (2009–2013). IgM measurements were performed every 6 months, and the data were averaged for each patient. We analyzed the frequency of exposure to clozapine treatment during the 5-year follow-up period as an exposition factor.

RESULTS

We investigated 33 patients who took clozapine and found 6 patients with SIgMD. We compared these patients with 67 patients not taking clozapine, of whom 2 had SIgMD. Of these 6 and 2 patients, we made a group of 8 case-patients with SIgMD. This group was compared with 92 (27 + 65) patients without SIgMD matched to cases on age, sex, weight, mental health unit, diagnosis, and psychiatric medication (Table 1). In both groups, there were patients who had taken clozapine: 6 of 8 in the SIgMD group (75%) and 27 of 92 in the non–SIgMD group (29%). We found an increased frequency of SIgMD among clozapine-treated patients (odds ratio = 7.2222; 95% CI, 1.3704–38.0623; $Z = 2.332$; $P = .0197$).

The side effect of agranulocytosis also may be a result of clozapine's immunosuppressant effect, but our results show no differences in granulocyte

Table 1. Characteristics of Cases and Controls[a]

Variable	Cases (n = 8)	Controls (n = 92)	*P* Value
Anthropometrics			
Male, n (%)	7 (88)	80 (87)	1.0000
Age, mean ± SD, y	49 ± 12	47 ± 13	1.0000
Height, mean ± SD, cm	174 ± 8	179 ± 15	.3555
Weight, mean ± SD, kg	85 ± 15	87 ± 19	.7728
Body mass index, mean ± SD, kg/m^2	28 ± 6	29 ± 6	.6522
Diagnoses (*DSM-IV*)			
Schizophrenia, n (%)	5 (63)	54 (59)	.6638
Bipolar disorder, n (%)	2 (25)	22 (24)	1.0000
Major depressive disorder, n (%)	0 (0)	3 (3)	.2462
Other psychotic disorders, n (%)	1 (12)	13 (14)	.1871
Psychiatric drugs			
Antidepressants, n (%)	2 (26)	30 (33)	.3523
Antipsychotics (clozapine included), n (%)	6 (75)	78 (85)	.1109
Benzodiazepines, n (%)	3 (38)	37 (41)	.7725
Lithium, n (%)	1 (13)	19 (21)	.1871
Laboratory values			
Immunoglobulin A level, mean ± SD, mg/dL	202 ± 80	214 ± 107	.7579
Immunoglobulin G level, mean ± SD, mg/dL	903 ± 195	991 ± 240	.3164
Immunoglobulin M level, mean ± SD, mg/dL	20 ± 3	100 ± 55	.0001*
White blood cell count, mean ± SD, cells/μL	7,115 ± 2,498	7,962 ± 2,772	.4060
Absolute neutrophil count, mean ± SD, cells/μL	4,117 ± 1,940	4,562 ± 2,007	.8341

[a]Student *t* test for comparing continuous variables; Fisher exact test for comparing categorical variables.
*Indicates statistical significance.

count between the 2 groups. Regarding the concomitant medications used by patients, a theoretically major confounding factor, no statistically significant difference in the distribution of antipsychotics other than clozapine,[5,6] anticonvulsants,[7] lithium,[8] and antidepressants[9] among cases and controls was observed (Table 1).

DISCUSSION

To date, there has been no other study analyzing an association between clozapine use and selective deficit of immunoglobulin. SIgMD does not occur in the literature as a side effect of other—typical or atypical—antipsychotics.

Our results demonstrate that health care professionals need to be vigilant with regard to the presence of SIgMD among clozapine-treated patients. In fact, patients affected by SIgMD require careful monitoring for infection and autoimmune diseases. Indeed, acute and chronic recurrent rhinosinusitis and allergic diathesis of the upper respiratory tract (eg, hay fever, allergic rhinitis, bronchial asthma, or atopic dermatitis allergies) are frequently observed in these patients and may require preventive and curative therapy.

A potential confounding factor relates to similar genetic abnormalities that are associated with SIgMD and schizophrenia (the most frequent diagnosis among cases and controls in our study). Indeed, deletion of chromosomal region 22q11.2 has been linked to some cases of SIgMD, and microdeletions occurring in this same chromosomal region have been reported to result in a 20- to 30-fold increased risk for schizophrenia. Although studies have suggested differential rates of 22q11.2 deletion syndrome in schizophrenia, the reported prevalence ranges from 0.5% to 2% (averaging approximately 1%).[10] Therefore, genetic deletion of 22q11.2 cannot fully account for the significant increase in SIgMD incidence rate that we observed in clozapine-treated schizophrenic patients.

Regarding the pathogenesis of this disorder, several mechanisms have been proposed to cause SIgMD, including enhanced regulatory T cell function, defective T helper cells, and impaired B lymphocyte differentiation.[11] Notably, clozapine appears to dysregulate both type-1 (eg, IL-2) and type-2 (eg, IL-10 and IL-6) cytokines and, consequently, affects B and T cells, which eventually may lead to the development of SIgMD. Despite these observations and the reviewed literature, the etiology of this disorder remains unclear.[12] However, whether SIgMD constitutes an unknown pharmacologic effect of clozapine or, alternatively, these individuals are part of a subset of patients affected by psychiatric disorders with psychotic symptomatology (eg, schizophrenia, bipolar disorder, major depressive disorder, and other psychotic disorders) who respond differently to antipsychotic drugs or display a different subpathology or endophenotype will require complementary studies.

We acknowledge that the findings of the present study are based on a small sample. Future investigations examining larger cohorts and with patient stratification controlling for major confounding factors will be required to validate this report. Nevertheless, our results indicate that clinicians should pay special attention to patterns of IgM decline and granulocyte counts among clozapine-treated patients.

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Drug names: clozapine (Clozaril, FazaClo, and others), lithium (Lithobid and others).

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