# Effect of clozapine on immunoglobulin M plasma levels

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Clozapine is an atypical antipsychotic medication indicated for the treatment of patients who fail to respond to standard antipsychotic treatment. It possesses immunomodulatory properties and requires regular counts of white blood cells and absolute neutrophils. It has been reported to mediate several effects on humoral immunity, such as altering the levels of antibody-producing cytokines [Hinze-Selch *et al.* 1998].

Selective immunoglobulin M immunodeficiency (SIgMD) is a rare form of dysgammaglobulinaemia characterized by a selective, low level of immunoglobulin M (IgM) in conjunction with normal T cell numbers and function, and with no other identifiable immunodeficiencies. It can occur as either a primary or secondary condition and displays an estimated prevalence of 0.03%–3%. Secondary SIgMD can be associated with malignancy, autoimmune disorders, gastrointestinal diseases and/or immunosuppressive treatments [Goldstein *et al.* 2006].

Here, we present a post hoc analisys based on data from a small case-control study designed to analyse the presence of SIgMD among clozapine-treated patients.

This case-control study took place among a cohort of psychiatric outpatients referred to the Mental Health Unit of the Hospital Real de Nuestra Señora de Gracia in Zaragoza, Spain. These patients underwent continuous psychiatric, immunological and biochemical monitoring over a 5-year follow-up period (2009–2013). The case group ($n$ = 8) consisted of all psychiatric outpatients who displayed selective SIgMD and a control group ($n$ = 92) consisting of randomly selected psychiatric outpatients matched to the cases on characteristics of age, sex, weight, mental health unit, diagnosis and psychiatric medication, and who had not displayed selective SIgMD (Table 1) [Lozano *et al.* 2015].

SIgMD was defined by mean IgM values ⩽20mg/dl (laboratory reference range of 40–230 mg/dl) maintained across the whole follow-up period and in conjunction with normal levels of immunoglobulin (Ig) A, IgG, white blood cell count and absolute neutrophil count. IgM measurements were performed every 6 months and the data were averaged for each subject [Lozano *et al.* 2015].

We determined plasma immunoglobulin M levels in all patients included in study and control groups. The study group was constituted of psychiatric outpatients who took clozapine for at least 5 years and, finally, we compared these patients with 67 psychiatric outpatients taking antipsychotics other than clozapine (control group). Student's t test was used to compare continuous variables and Fisher's exact test for comparing categorical variables (Table 1). We found an increased frequency of SIgMD among psychiatric clozapine-treated patients [5 clozapine-treated patients (14 %) vs 0 No-clozapine-treated patients (0%); 95% CI of difference= 0.0355-0.32677; $p$ = 0.0032]. with an overall decrease of mean plasma levels of IgM in the study group compared to control group. No differences between groups with respect to IgA, IgG, absolute neutrophil count and white blood cell count were observed.

Whether this is due to an unknown pharmacological effect of clozapine or if, alternatively, these individuals are part of a subset of psychiatric patients who respond differently to antipsychotic drugs and/or display a different subpathology or endophenotype will require complementary studies.

However, our results suggest that healthcare professionals must be vigilant with regard to the presence of SIgMD and/or decrease of IgM plasma levels among clozapine-treated patients. The

**Table 1.** Characteristics of patients in each group.

| Variable | Cases $n = 8$ | control group (NO clozapine-treated) $n = 67$ | $p$ value |
|---|---|---|---|
| Anthropometric | | | |
| Male sex, no. of patients (%) | 13 (38) | 27 (41) | 1.00 |
| Age, years | 44 ± 10 | 47 ± 14 | 0.27 |
| Height, cm | 175 ± 31 | 167 ± 21 | 0.13 |
| Weight, kg | 99 ± 21 | 81 ± 18 | <0.01 |
| Body mass index, kg/m$^2$ | 31 ± 6 | 29 ± 6 | 0.12 |
| Diagnosis (DSM-IV) | | | |
| Schizophrenia | 19 (58) | 40 (60) | 1.00 |
| Bipolar disorder | 8 (24) | 16 (24) | 1.00 |
| Major depressive disorder | 1 (3) | 2 (3) | 1.00 |
| Other psychotic disorders | 5 (15) | 9 (13) | 1.00 |
| Psychiatric drug treatment | | | |
| Antidepressants | 12 (36) | 20 (30) | 0.65 |
| Antipsychotics (other than clozapine) | 0 (0) | 67 (100) | <0.01 |
| Clozapine | 33 (100) | 0 (0) | <0.01 |
| Benzodiazepines | 13 (39) | 27 (40) | 1.00 |
| Lithium | 5 (15) | 9 (13) | 1.00 |
| Results | | | |
| IgA level, mg/dl | 189 ± 100 | 221 ± 131 | 0.22 |
| IgG level, mg/dl | 1,009 ± 269 | 1,005 ± 216 | 0.94 |
| **IgM level, mg/dl** | **79 ± 59** | **114 ± 69** | **0.014** |
| White blood cell count, cells/µl | 7,862 ± 2,593 | 8.027 ± 2,798 | 0.74 |
| Absolute neutrophil count, cells/µl | 4,762 ± 1.962 | 4.607 ± 2,027 | 0.72 |

Student's *t* test was used to compare continuous variables and Fisher's exact test for comparing categorical variables.
Mean ± standard deviation; numbers in brackets are percentages.
DSM-IV, Diagnostic and Statistical Manual of Mental Disorders IV; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M.

patients affected by SIgMD and/or decrease of IgM plasma levels require careful monitoring for infection and/or autoimmune diseases. Indeed, acute/chronic recurrent rhinosinusitis and allergic diathesis of the upper respiratory tract (e.g. hay fever, allergic rhinitis, bronchial asthma or atopic dermatitis allergies) are frequently observed in these patients and may require preventive and/or curative therapy.

A potential confounding factor relates to some similar genetic abnormalities that are associated with both SIgMD and/or decrease of IgM plasma levels and schizophrenia (the most frequent diagnosis among cases and controls). Indeed, deletion of chromosomal region 22q11.2 has been linked to some cases of SIgMD and/or decrease of IgM plasma levels, and microdeletions occurring in this same chromosomal region have been reported to result in a 20–30 fold increase in the 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%) [Horowitz *et al.* 2005]. Therefore, genetic deletion of 22q11.2 cannot fully account for the significantly increased rate of SIgMD and/or decrease of IgM plasma levels we observed among the clozapine-treated patients.

Regarding the pathogenesis of this disorder, several mechanisms have been proposed as causing decrease of IgM plasma levels, including enhanced regulatory T-cell function, defective T helper cells and impaired B lymphocyte differentiation [Yel *et al.* 2009]. Notably, clozapine appears to disregulate both type 1 [e.g. interleukin (IL) 2: subchronic treatment with clozapine increasing sIL-2R levels] and type 2 (e.g. IL-10 and IL-6) cytokines. However, the IL2Rα and β genes are localized in the 22q11.2-q12 chromosome region, the deletion of which causes

DiGeorge syndrome. Despite all these data, the aetiology of this disorder, which is characterized by recurrent infections and autoimmunity, remains unclear [Kluge *et al.* 2009].

We acknowledge that our findings might not be applicable to all psychiatric clozapine-treated patients, as the present study was based on a small sample. Therefore, future investigations examining larger cohorts and stratifying patient study groups according to psychiatric medication and other major confounding factors (e.g. psychiatric diagnoses, deletion of and microdeletions in chromosomal region 22q11.2) 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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## Conflict of interest statement

The authors declare no conflict of interest in preparing this letter.



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