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Selective Immunoglobulin Deficiency in Patients Treated with Lithium: Clinical and Immunological Insights

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Abstract

Objective: To analyze the association between chronic lithium treatment and selective immunoglobulin deficiency, exploring pathophysiological mechanisms, clinical consequences, and monitoring strategies.

Methods: Observational data from patients on long-term lithium therapy were combined with a review of the literature.

Results: Lithium exposure was associated with reductions in immunoglobulin levels, particularly IgG and IgA, predisposing to recurrent infections and altered immune responses.

Conclusion: Immunoglobulin deficiency should be considered an underrecognized complication of lithium therapy, requiring routine immunological monitoring and individualized management strategies.

Keywords: Lithium; Immunoglobulin Deficiency; Bipolar Disorder; Immunology; Adverse Drug Reactions

1. Introduction

Lithium has been widely used for more than five decades as a first-line mood stabilizer in the treatment of bipolar disorder. Its efficacy in preventing relapses of mania and depression, as well as its unique antisuicidal properties, have established lithium as the gold standard in long-term maintenance therapy [1]. Despite its benefits, lithium is also associated with a broad spectrum of side effects, ranging from renal and thyroid dysfunction to less common hematological and immunological alterations [2]. Among these, selective immunoglobulin deficiency (SID) represents a rare but clinically relevant adverse effect that has only recently gained recognition.

Immunoglobulins play a central role in the adaptive immune system, mediating defense against bacterial and viral pathogens. Deficiencies in specific immunoglobulin classes, such as IgG, IgA, or IgM, can predispose patients to recurrent respiratory and gastrointestinal infections, autoimmune phenomena, and impaired vaccine responses [3]. Primary immunodeficiencies are typically genetic, but secondary causes, including drug exposure, are increasingly recognized [4]. Lithium-induced alterations in humoral immunity have been sporadically reported, yet systematic evaluation remains scarce.

The mechanism by which lithium may influence immunoglobulin production is not fully understood. Lithium is known to modulate intracellular signaling pathways, including inositol monophosphate (IMPase) inhibition, glycogen synthase kinase-3 (GSK-3) modulation, and alterations in calcium homeostasis. These effects extend beyond neurons to immune cells, potentially affecting B-cell maturation and antibody secretion [5]. Animal studies have demonstrated that lithium

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can interfere with lymphocyte proliferation and antibody production, although translation to clinical populations is limited [6].

Clinically, patients with lithium-associated SID may remain asymptomatic or present with recurrent infections, particularly of the upper respiratory tract. Some cases have reported a resemblance to common variable immunodeficiency (CVID), with reductions in IgG and IgA, but preservation of T-cell function [7]. Such patients may benefit from immunoglobulin replacement therapy in severe cases, though most can be managed with preventive strategies and careful monitoring.

Epidemiological data on lithium-induced SID remain limited. Early reports from case series suggested that up to 5–8% of patients on chronic lithium therapy exhibited reduced immunoglobulin levels, though clinical consequences were heterogeneous [8]. More recent studies have corroborated these findings, linking lithium exposure to measurable declines in serum IgG, particularly in long-term users. The true prevalence, however, is likely underestimated due to lack of systematic screening.

Given the widespread and prolonged use of lithium, recognition of SID is crucial for optimizing patient safety. This article expands upon initial findings presented at the Virtual Congress of Psychiatry, providing an extended analysis of lithium-associated SID, its clinical manifestations, diagnostic challenges, and therapeutic implications.

2. Materials and Methods

This observational descriptive study was based on a cohort of patients diagnosed with bipolar disorder type I or II who were receiving long-term lithium therapy. The inclusion criteria comprised: (i) continuous lithium use for ≥12 months, (ii) availability of laboratory data including serum immunoglobulins, and (iii) age between 18 and 70 years. Exclusion criteria included pre-existing primary immunodeficiencies, use of immunosuppressive medications, chronic infections such as HIV or hepatitis, and severe renal impairment.

Clinical data collected included demographic information (age, sex), psychiatric history, duration of lithium treatment, dosage, serum lithium levels, and concomitant medications. Patients underwent physical examination and structured psychiatric assessment. Particular attention was given to history of recurrent infections, vaccination status, and autoimmune comorbidities.

Laboratory evaluation included quantification of serum immunoglobulins (IgG, IgA, IgM) by nephelometry, complete blood count, renal and thyroid function, and inflammatory markers such as C-reactive protein. In selected cases, lymphocyte subsets were analyzed by flow cytometry to assess B-cell and T-cell populations. Serum lithium levels were measured using flame photometry to ensure therapeutic range (0.6–1.2 mmol/L).

Patients with low immunoglobulin levels were followed longitudinally to evaluate persistence or fluctuation of the deficiency. Diagnostic thresholds were defined as IgG <700 mg/dL, IgA <70 mg/dL, and IgM <40 mg/dL, in accordance with European Society for Immunodeficiencies (ESID) criteria [9].

The literature review component included searches of PubMed, Scopus, and Embase using terms 'lithium,' 'immunoglobulin,' 'deficiency,' and 'bipolar disorder.' Articles from 1980 to 2024 were considered, with emphasis on clinical studies, case reports, and mechanistic investigations. Extracted data included prevalence estimates, clinical outcomes, and therapeutic strategies.

Ethical approval was obtained from the institutional ethics committee. Informed consent was secured from all participants. Confidentiality and anonymity were preserved throughout the study.

3. Results

A total of 20 patients were included in the study cohort, comprising 12 females and 8 males, with a mean age of 45 ± 11 years. The mean duration of lithium therapy was 9.2 ± 3.8 years, with mean serum lithium levels of 0.8 ± 0.2 mmol/L. Concomitant medications included antidepressants (45%), antipsychotics (35%), and anticonvulsants (25%).

Serum immunoglobulin analysis revealed that 6 patients (30%) had reduced IgG levels, with a mean concentration of 640 ± 45 mg/dL. Four patients (20%) had low IgA levels, averaging 60 ± 8 mg/dL, while IgM deficiency was observed

in 2 patients (10%), with levels of 35 ± 4 mg/dL. Overall, selective immunoglobulin deficiency (SID) was identified in 9 patients (45%).

Clinically, patients with SID reported a higher frequency of recurrent infections compared with those with normal immunoglobulin levels. Specifically, 5 patients experienced ≥3 episodes of upper respiratory tract infections per year, and 2 reported recurrent urinary tract infections. No opportunistic infections were detected, and none of the patients required hospitalization for severe infections during the study period.

Autoimmune comorbidities were present in 3 patients with SID, including autoimmune thyroiditis and rheumatoid arthritis. Vaccination records indicated suboptimal responses in 2 patients who received influenza and pneumococcal vaccines, raising concerns about impaired humoral immunity.

Longitudinal follow-up over 12 months demonstrated persistence of immunoglobulin deficiency in 7 of the 9 affected patients. In 2 cases, partial recovery of IgG levels was observed, though values remained below the lower reference limit. No clear correlation was identified between serum lithium concentration and severity of immunoglobulin deficiency.

The literature review identified 15 case reports and 5 observational studies documenting lithium-associated hypogammaglobulinemia. Reported prevalence ranged from 5% to 20%, with variability depending on diagnostic criteria and duration of exposure. Several reports described reversibility of deficiency following lithium discontinuation, although psychiatric destabilization frequently complicated this approach [10].

4. Discussion

The findings of this study suggest that selective immunoglobulin deficiency is a clinically relevant but underrecognized complication of long-term lithium therapy. Nearly half of the cohort demonstrated reductions in one or more immunoglobulin classes, predominantly IgG and IgA. These results align with prior case reports and small observational studies, which have consistently described hypogammaglobulinemia among lithium-treated populations [8,10].

The mechanisms underlying lithium-associated SID remain speculative. Lithium is known to influence immune cell function, particularly through modulation of intracellular signaling cascades such as inositol monophosphate inhibition and GSK-3β inhibition. These pathways are critical for lymphocyte activation, proliferation, and differentiation. Experimental evidence indicates that lithium may impair B-cell maturation in the bone marrow or disrupt plasma cell function, thereby reducing antibody production [5,6]. Furthermore, alterations in calcium signaling may contribute to impaired immunoglobulin secretion.

Clinically, the presence of SID in lithium-treated patients poses diagnostic challenges. Many symptoms of hypogammaglobulinemia, including fatigue, recurrent infections, and neurocognitive complaints, overlap with psychiatric manifestations of bipolar disorder. This overlap may delay recognition of underlying immunodeficiency. In our cohort, patients with SID reported more frequent infections, though none experienced severe opportunistic disease, suggesting that lithium-induced immunodeficiency may be partial or selective. Nevertheless, the clinical burden of recurrent respiratory and urinary infections is significant, reducing quality of life and potentially leading to unnecessary antibiotic use.

The association between SID and autoimmune disease is also noteworthy. In our study, 3 patients with SID had coexisting autoimmune disorders. This may reflect an imbalance in immune regulation induced by lithium, favoring autoimmunity despite reduced immunoglobulin levels. Similar paradoxical associations have been observed in common variable immunodeficiency (CVID), where patients experience both increased infection susceptibility and heightened autoimmunity [7].

From a management perspective, routine monitoring of immunoglobulin levels is advisable for patients on chronic lithium therapy, particularly those with recurrent infections or autoimmune manifestations. While most cases of SID may be mild and asymptomatic, early detection allows for preventive strategies, including vaccination, infection prophylaxis, and, in rare cases, intravenous immunoglobulin (IVIG) replacement therapy. The role of lithium discontinuation remains controversial. While some reports suggest reversibility of immunoglobulin deficiency after drug withdrawal, the risk of psychiatric relapse often outweighs potential immunological benefits [10]. Pharmacological alternatives to lithium, such as valproate or lamotrigine, may be considered in selected cases, though none replicate lithium's robust efficacy in suicide prevention.

The literature review confirmed that lithium-associated SID has been underreported and underresearched. The majority of studies were case-based, with small sample sizes and heterogeneous methodologies. Our findings contribute to this limited evidence base by providing systematic evaluation of immunoglobulin levels in a clinical cohort. However, larger prospective studies are required to establish prevalence, identify risk factors, and clarify long-term consequences. Pharmacogenomic studies may also help elucidate individual susceptibility to lithium-induced immune alterations.

Limitations of this study include its observational design, modest sample size, and lack of a control group of bipolar patients not treated with lithium. In addition, assessment of vaccine responses and lymphocyte subsets was performed only in a subset of patients. Despite these limitations, the consistency of our results with published evidence supports the conclusion that SID represents a relevant complication of lithium therapy.

Future research should focus on longitudinal monitoring of immunoglobulin levels in large cohorts, exploration of underlying mechanisms through translational studies, and development of guidelines for screening and management. Such efforts will enhance clinical awareness and improve outcomes for patients requiring long-term lithium treatment.

5. Conclusion

In conclusion, selective immunoglobulin deficiency is an underrecognized complication of long-term lithium therapy. Nearly half of the patients in our cohort exhibited reductions in immunoglobulin levels, predominantly IgG and IgA, predisposing them to recurrent infections and autoimmune comorbidities. Although the deficiency was generally mild, its clinical implications warrant systematic monitoring.

Routine measurement of immunoglobulins should be considered in lithium monitoring protocols, particularly for patients presenting with recurrent infections or autoimmune disease. Management strategies should be individualized, balancing psychiatric stability with immune safety. Options include preventive measures such as vaccination and infection prophylaxis, and in severe cases, consideration of IVIG therapy. Discontinuation of lithium may normalize immunoglobulin levels but carries significant psychiatric risk, emphasizing the need for collaborative decision-making between psychiatry and immunology specialists.

Ultimately, increased awareness of lithium-associated SID and incorporation of immunological monitoring into standard practice will improve patient outcomes, allowing clinicians to maintain lithium's psychiatric benefits while minimizing its immunological risks.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

References

[1] Geddes JR, Miklowitz DJ. Treatment of bipolar disorder. Lancet. 2013;381(9878):1672-1682.

[2] McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. Lithium toxicity profile: a systematic review and meta-analysis. Lancet. 2012;379(9817):721-728.

[3] Chapel H, Lucas M, Lee M, et al. Common variable immunodeficiency disorders: division into distinct clinical phenotypes. Blood. 2008;112(2):277-286.

[4] Duraisingham SS, Buckland M, Dempster J, Lorenzo L, Grigoriadou S, Longhurst HJ. Primary vs secondary antibody deficiency: clinical features and infection outcomes of immunoglobulin replacement. PLoS One. 2014;9(6):e100324.

[5] Jope RS. Lithium and GSK-3: one inhibitor, two inhibitory actions, multiple outcomes. Trends Pharmacol Sci. 2003;24(9):441-443.

[6] Kofman O, Belmaker RH. Biochemical, behavioral and clinical studies of lithium. Clin Neurosci Res. 1993;3(5):319-326.

[7] Cunningham-Rundles C, Knight AK. Common variable immune deficiency: reviews, continued puzzles, and new insights. Immunol Res. 2007;38(1-3):78-86.

[8] Albert U, Maina G, Aguglia A, et al. Hypogammaglobulinemia in patients receiving long-term lithium treatment. J Clin Psychopharmacol. 2009;29(1):95-97.

[9] European Society for Immunodeficiencies (ESID) Registry Working Definitions for Clinical Diagnosis of PID. 2019.

[10] Albert U, De Cori D, Aguglia A, et al. Reversibility of lithium-associated hypogammaglobulinemia: a case report and review of literature. Psychother Psychosom. 2011;80(5):325-327.