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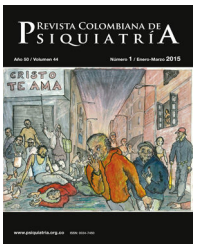

Reporte de caso

Clozapine-Induced Eosinophilia: a Case Report

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ABSTRACT

Introduction: Clozapine is an atypical antipsychotic drug eligible for treatment-resistant schizophrenia. It frequently represents the best and the only choice in resistant schizophrenia. However, its use is feared by many professionals due to its possible adverse effects, such as eosinophilia.
Case report: We report a case of a young white male suffering from treatment-resistant schizophrenia who rapidly developed eosinophilia after starting clozapine.
Discussion: We present a case of a 26-year-old white man diagnosed with schizophrenia with poor clinical response to several antipsychotics owing to which clozapine was started. Psychotic symptoms improved dramatically but a progressively ascendant eosinophilia was reported during serial haematological analyses. The patient remained physically asymptomatic. An exhaustive assessment with ancillary diagnostic tests revealed no cause for eosinophilia. Thus, a diagnosis of clozapine-induced eosinophilia was made. The drug was discontinued and eosinophil count progressively returned to normal but psychotic symptoms worsened.
Conclusions: Clozapine treatment is frequently feared due to its possible side effects and complications, delaying its use in refractory schizophrenia. Also, to our knowledge, there are no specific guidelines on how to manage haematological side effects such as eosinophilia. This is problematic as, in some cases, it may lead to an unnecessary withdrawal of clozapine with a worsening of psychotic symptoms. We present a brief discussion of the recent literature on the subject.

Eosinofilia Inducida por Clozapina: un Caso Clínico

Palabras clave:
Eosinofilia inducida por clozapina
Eosinofilia

RESUMEN

Introducción: La clozapina es un fármaco antipsicótico atípico eligible para la esquizofrenia resistente al tratamiento. Con frecuencia representa la mejor y la única opción para la esquizofrenia resistente. Sin embargo, muchos profesionales temen utilizarla por sus posibles efectos adversos, como la eosinofilia.

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Clozapina
Esquizofrenia

Reporte de caso: Se expone el caso de un joven blanco que sufre esquizofrenia resistente al tratamiento y desarrolló eosinofilia rápidamente tras comenzar el tratamiento con clozapina.

Discusión: Varón de 26 años con diagnóstico de esquizofrenia y mala respuesta clínica a varios antipsicóticos, por lo que se inició clozapina. Los síntomas psicóticos mejoraron drásticamente, pero los análisis hematológicos seriados informaron una eosinofilia en ascenso progresivo. El paciente permaneció físicamente asintomático. Una evaluación exhaustiva con pruebas de diagnóstico complementarias no reveló ninguna causa de eosinofilia. Por lo tanto, se diagnosticó eosinofilia inducida por clozapina. Se suspendió el fármaco, el recuento de eosinófilos volvió progresivamente a la normalidad, pero los síntomas psicóticos empeoraron.

Conclusiones: A menudo se teme tratar con clozapina por sus posibles efectos secundarios y sus complicaciones, lo cual retrasa su uso en la esquizofrenia refractaria. Además, hasta donde sabemos, no existen pautas específicas sobre cómo tratar los efectos secundarios hematológicos como la eosinofilia. Esto es problemático porque, en algunos casos, puede conducir a suspender innecesariamente la clozapina y que empeoren los síntomas psicóticos. Se presenta una breve discusión de la literatura reciente sobre el tema.

Introduction

Clozapine is an atypical antipsychotic eligible for treatment-resistant schizophrenia.[1] It is frequently the best and the only pharmacologic choice in resistant schizophrenia. However, its use is feared by many professionals due to its possible adverse effects, like eosinophilia.

Case report

A schizophrenic white 26-years-old man was seen in acute setting for behavioural changes. He presented a poor and disorganized speech, mystical, persecutory, and messianic delusions, auditory hallucinations, soliloquies, and unmotivated laughter. Due to these symptoms and his lack of insight, he was compulsively hospitalized. He had history of oppositional disorder diagnosed in adolescence, poor therapeutic adhesion, mild cognitive impairment, allergic rhinitis, egg allergy and cannabinoids abuse since the age of 20.

The diagnostic workup including EKG, a thorough blood and urine test, brain CAT scan showed no abnormalities.

After several weeks, his symptoms did not improve despite several trials with a combination of antipsychotics. A diagnosis of treatment-resistant schizophrenia was considered, and clozapine titration was started with close haematology monitoring. A progressive and significant psychopathological improvement was observed.

Thirteen days after clozapine was initiated, eosinophil count increased to 600/cmm. Titration of clozapine was suspended, and its dose was kept stable. Patient was physically asymptomatic and presented no other analytical changes. However, eosinophil count kept increasing, peaking 7900/cmm (53% of total leucocyte count) on the sixteenth day of treatment. Clozapine and all medications that could also induce eosinophilia, according to the available literature, were suspended. The eosinophil count remained increasing in the next five days before gradually returning to the reference values one week later.

A clinical exhaustive evaluation by Internal Medicine revealed no cause for eosinophilia.

Therefore, a diagnostic of a clozapine-induced eosinophilia was made.

Patient was discharged home two and half months after admission medicated with lorazepam 7.5 mg per day and haloperidol 5 mg per day. His behaviour was stable but residual delusional symptoms persisted.

Discussion

Clozapine is a second generation antipsychotic eligible for treatment-resistant schizophrenia, suicide risk in patients with schizophrenia spectrum disorders, aggressiveness or violence in psychiatric patients, comorbid substance abuse, psychosis in Parkinson's disease, and prevention and treatment of tardive dyskinesia.[1]

It is frequently the best, and unfortunately the only, choice in resistant schizophrenia, being considered in this context superior to other antipsychotics.[2]

Initially developed in the early 1970's but its use rapidly decreased after reported cases of treatment-induced, fatal, agranulocytosis,[3] perhaps the most feared side effect of clozapine in the world. Despite this, it is not the most common adverse effect, affecting just 0.8% of patients receiving their therapy.[3]

The use of clozapine is associated with numerous adverse effects, involving up to 76% of patients treated and which motivates stopping treatment in 17% of cases.[1] The most common adverse effects include agranulocytosis,

convulsions, sialorrhea, orthostasis, tachycardia, constipation, and somnolence.[1] Pancreatitis, hepatitis, colitis, nephritis, and myocarditis have also been described.[4]

Eosinophilia is a relatively common, non-dose-dependent adverse effect of clozapine treatment, usually during the first year, mainly the first four weeks.[1,3,5] The reported incidence varies significantly, ranging from 1 to 13%.[1,5,6] The largest study, with 2404 patients, in Italy, found the incidence of 2.2%.[7]

Clozapine-induced eosinophilia seems to be linked, according to various authors, to allergic immunological phenomena including type I hypersensitivity reaction and stimulation of T lymphocytes, however the etiopathogenesis is still unknown.[1,2,4,5,8]

In agreement with several authors, most cases of eosinophilia during clozapine treatment are transient[9] and, in recent literature, have been defined as "benign" eosinophilia in contrast to cases of eosinophilia linked to systemic inflammation and organ damage.

However, in some cases, the onset of eosinophilia may predict subsequent neutropenia, myocarditis, eosinophilic colitis, pancreatitis and toxic hepatitis,[1,5] therefore the association with possible more serious inflammatory processes makes it more difficult to weigh the right conduct in spite of this clinical situation.

Despite this, most cases of eosinophilia during clozapine treatment are transient and self-limiting[9] and, in recent literature, have been defined as "benign" eosinophilia in contrast to cases of eosinophilia linked to systemic inflammation and organ damage. In "benign eosinophilia", occurs in asymptomatic patients with no systemic inflammation, it is widely believed that the withdrawal of the drug is not necessary and that close monitoring of the patient is enough.[1,8]. Many of these cases can resolve spontaneously without stopping treatment[4,8,10]; indeed, many successful cases have also been described both in continuing treatment in patients who develop eosinophilia, and in restarting treatment in patients with a history of clozapine-induced eosinophilia.[2-4,6,8,11,12]

Conclusions

Currently, there are no specific guidelines on the management of hematological side effects like eosinophilia. The only indications available now are those of the manufacturer, which suggests stopping the treatment when the eosinophil count is higher than 3×10^9 and possibly restart when it is below 1×10^9. Several experts have suggested in recent years that the risk of discontinuing therapy, when all other medical conditions have been ruled out, outweighs any benefits.[13]

In the patient under examination, during the hospitalization, we decided to follow the manufacturer's instructions, therefore, withdraw the clozapine. At the time of discharge, there was doubt about the possibility of the patient try to hide part of his productive symptoms. He was in a long-term hospitalization, tired, and already without criteria for compulsive hospitalization than he was discharged and oriented for internal medicine and psychiatry ambulatory follow-up.

Recently, he was discharged from the internal medicine consultation definitively ruled out any other medical condition possibly causing the reported clinical case. Regarding psychiatric follow-up, cognitive decline, and loss of functionality as well as the prevalence of negative symptoms remains evident in this patient. Actually, he is relatively under-medicated compared to the case initially presented, which may be due, in our opinion, mainly to a defensive posture towards the interviewer, in order to avoid new admissions, which in our experience is not uncommon.

For this reason, it maintains a tight ambulatory control without ruling out the possibility of a new rechallenge with clozapine or referral for electroconvulsive therapy.

Faced with the recent literature, we agree with the many authors who recommend the continuation of clozapine therapy when eosinophilia exists in the absence of symptoms and no evidence of systemic inflammation and organ damage.

Today, treatment-resistant schizophrenia accounts for about one third of patients with schizophrenia[11] and, faced with the lack of therapeutic responses,[2] it is necessary to make the best use of the available resources. In the case of clozapine, therefore, the correct description and definition of adequate management of any adverse effects is essential. As many authors have pointed out, this would prevent our patients from unnecessary loss of therapeutic opportunities[3] and, consequently, of their quality of life.

We reinforce the idea that the decision to stop clozapine treatment must be made based on patient's clinical and analytical evolution[12] considering the highly unfavorable cost-benefit ratio that *a priori* withdrawal of medication has.

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