Letter to the editor

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Clozapine-induce myocarditis

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Clozapine is an atypical antipsychotic drug derived from dibenzodiazepines, with weak D_2 dopamine receptor activity and high affinity for the D_1 and D_4 dopamine receptors in addition to potent serotoninergic and noradrenergic antagonism. It is the only atypical antipsychotic with established efficacy in patients diagnosed of resistant schizophrenia, it being effective in 30% of schizophrenic patients refractory to other treatments.[1]

However, clozapine has multiple side effects, some of which are potentially lethal. Among others, induction of agranulocytosis in 1% of the patients treated in the first year of treatment[2] which is why blood monitoring is obligatory as well as seizures, pulmonary thromboembolism, hyperglycemia and hepatitis stand out.[3] Cardiac complications such as myocarditis and cardiomyopathy have always been closely related with treatment with clozapine[4] and have been described in direct relationship with the drug.[5] Well-documented information and cases exist that show a strong association between the drug and this adverse effect, but not with other antipsychotic drugs.[6] The first case of myocarditis due to clozapine was published in 1980 by Vesterby et al.[7] However, this association was not confirmed until 1999 when Killian et al. identified 15 cases of myocarditis and 8 of cardiomyopathy among 8000 patients treated with clozapine.[8] A current incidence of 0.7%-1.2% has been estimated[9] and the presence of myocarditis from the third to sixth week of treatment has been reported.[5,8] There is a greater risk of developing cardiac alterations during the first month, however this risk persists with its use.[8,10] There is also a greater risk of chronic cardiomyopathy between the second month and three years after the initiation of the treatment,[10] with the possibility that a non-fulminant myocarditis picture or even a subclinical one will progress towards dilated cardiomyopathy over the years.[3]

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We present the case of a 26-year old male diagnosed of paranoid schizophrenia who presented symptoms refractory to multiple antipsychotic treatments with haloperidol, olanzapine, risperidone and amisulpride, used at correct doses and times, so that treatment was initiated with clozapine. On admission, the complete blood count and rest of the basic laboratory analyses were normal. The chest X-ray and electrocardiogram , showing sinus rhythm at 88 bpm, were also normal. Treatment was initiated at 25 mg/day, with increases of 25 mg/day every 48 hours. Fifteen days after initiating the treatment, coinciding with the increase of the dose from 150 to 175 mg/day, the patient presented generalized malaise, myalgias, non-productive cough, sinus tachycardia (120 bpm), respiratory distress, tachypnea and 39.5 ºC fever that did not abate with antithermic treatment. Cardiopulmonary auscultation showed a decrease of bilateral vesicular murmur. The blood gases indicated hypoxemia (pO_2 of 54 mmHg and pCO_2 of 34.3 mmHg). The complete blood count values showed neutrophils 68%, lymphocytes 18% and eosinophilia 4%. An enlarged cardiopericardial silhouette with bilateral pleural effusion, consistent with heart failure, was observed in the chest X-ray. The patient was sent to the internal medicine department where an ECG was performed (microcomplexes with T wave inversion in DI, DII and DIII) and the echocardiogram (left ventricle with normal diameters, with depression of systolic function and 45% ejection fraction). Blood cultures were negative. Seriated analyses showed neutrophilia (68% to 74%) with eosinophilia (from 4% to 11% of eosinophils). The diagnostic impression was myocarditis with probable drug etiology. Withdrawal of clozapine was indicated and treatment was prescribed with furosemide 60 mg/day, losartan potassium 50 mg/day and enalapril 5 mg/day, with good evolution of the clinical picture. At 10 days, the echocardiogram showed recovery of the systolic function and an EF of 69% with normalization of the complete blood count, so that new psychiatric treatment was established: haloperidol 12 mg/day, biperiden 4 mg/day and lamotrigine 100 mg/day.

Many theories have tried to uphold the nature of clozapine-induced myocarditis. Due to the presence of eosinophilic and eosinophilia infiltrates in peripheral blood, an acute IgE

mediated (allergic type I reaction) hypersensitivity reaction to the drug has been proposed.[5,8] Other pathogenic theories imply a type III allergic reaction with the formation and precipitation of immunocomplexes, although damage only in the cardiac muscle is uncommon,[8] or due to a direct toxic effect of the clozapine in the cardiac muscle by inflammatory infiltrates[8] or drug-induced increase of catecholamines and cytokines.[11] However, these hypotheses have still not been proven. As this case shows, the clinical characteristics of myocarditis are nonspecific. Although symptoms such as fever, tachycardia, chest pain, dyspnea, eosinophilia, elevated cardiac enzymes and changes in the ECG may be present, none of these are pathognomonic of the picture.[3] In addition, many characteristics of the myocarditis –fever, tachycardia or fatigue– may also be present due merely due to treatment with clozapine. The resolution of the symptoms in days or weeks is common in the patients who survive the first phases and the improvement of heart function may be delayed over time.[5]

When this clinical picture is suspected, it is urgent to carry out careful monitoring of the cardiac function, evaluation of the clinical symptoms compromising the cardiac function (palpitations, chest pain, dyspnea), signs of autoimmune response (fever, leukocytosis, eosinophilia), direct signs of myocardial injury (elevation of CK, LDH, AST) and signs of cardiac dysfunction using techniques such as ECG and echocardiography. In addition, clozapine must be immediately discontinued, initiating the corresponding cardiological treatment.

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