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CASO CLÍNICO: ÚLCERAS EN LAS PIERNAS QUE SE RESUELVEN DESPUÉS DE SUSPENDER LA CLOZAPINA PARA LA ESQUIZOFRENIA

CASE REPORT: LEG ULCERS RESOLVING AFTER DISCONTINUATION OF CLOZAPINE FOR SCHIZOPHRENIA

CASO CLÍNICO: RESOLUÇÃO DE ÚLCERAS DOS MEMBROS INFERIORES APÓS DESCONTINUAÇÃO DE CLOZAPINA PARA ESQUIZOFRENIA

C. Fragoeiro[1], C. Machado[1], P. Moura Ferreira[2]

[1]Médica Residente de Psiquiatría en el Hospital de Magalhães Lemos, Porto, Portugal
[2]Médico Psiquiatra en el Hospital de Magalhães Lemos, Porto, Portugal

Correspondencia: Cristina Fragoeiro, CristinaFragoeiro@hmlemos.min-saude.pt, Rua Professor Álvaro Rodrigues 4149-003 Porto

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LEER

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RESUMEN

Hay una alta prevalencia de afecciones cutáneas y alteraciones metabólicas en pacientes con esquizofrenia. Las úlceras cutáneas, en particular las de las extremidades inferiores, son el resultado más común de patología arterial y / o venosa. La diabetes se considera también un factor de riesgo importante. Los antipsicóticos atípicos están associados a un mayor riesgo de efectos secundarios cardiometabólicos y la clozapina se encuentra entre los de mayor riesgo.

Presentamos el reporte de caso de una paciente de 57 años con esquizofrenia refractaria que recibió como tratamiento una combinación de clozapina y haloperidol. En asociación con la introducción de clozapina, la paciente desarrolló diabetes mellitus tipo 2 y poco después han surgido ulceraciones maleolares persistentes. Con la suspensión de la clozapina las úlceras definitivamente se resolvieron. Por último, discutimos la patofisiología subyacente à las úlceras y presentamos los resultados de una revisión de la literatura sobre los efectos secundarios metabólicos y cutáneos de los antipsicóticos. Según sabemos, este es el primer reporte de caso de un paciente que desarrolló úlceras en las piernas tras el tratamiento con clozapina.

Palabras clave: Fármacos antipsicóticos, clozapina, efectos secundarios de fármacos, úlcera.

ABSTRACT

There is a high prevalence of skin conditions and metabolic disturbances in patients with schizophrenia. Skin ulcers, in particular those of the lower extremities, mostly arise from arterial and/or venous pathology. Diabetes is considered a prominent risk factor. Atypical antipsychotics carry an increased risk for cardiometabolic side effects, clozapine being among those with the highest risk.

We explore the case of a 57-year-old female patient with refractory schizophrenia who received a combination of clozapine and haloperidol. She soon developed type 2 diabetes mellitus and persistent malleolar ulcerations shortly thereafter. We discontinued clozapine and the ulcerations resolved definitively. We discuss underlying ulcer pathophysiology and review the literature for metabolic and cutaneous side effects of antipsychotics. To our knowledge, this is the first report of a patient developing leg ulcers upon treatment with clozapine.

Keywords: Antipsychotic Agents, Clozapine, Drug-Related Side Effects and Adverse Reactions, Ulcer.

RESUMO

Há uma elevada prevalência de condições dermatológicas e alterações metabólicas nos doentes com esquizofrenia. Úlceras cutâneas, em particular as dos membros inferiores, surgem maioritariamente por patologia arterial e/ou venosa. A diabetes é considerada um fator de risco importante. Os antipsicóticos atípicos têm um maior risco de efeitos laterais cardiometabólicos, a clozapina entre os que acarretam maior risco.

Exploramos o caso de uma doente de 57 anos com esquizofrenia refractária que foi tratada com uma combinação de clozapina e haloperidol. Desenvolveu diabetes mellitus tipo 2 e, pouco depois, úlceras meleolares persistentes. Descontinuamos a clozapina e as úlceras resolveram definitivamente. Discutimos a patofisiologia subjacente e revemos a literatura para efeitos laterais metabólicos e cutâneos de antipsicóticos. Do nosso conhecimento, este é o primeiro relato de uma doente a desenvolver úlceras dos membros inferiores com o tratamento com clozapina.

Keywords: Fármacos antipsicóticos, clozapina, efeitos laterais de fármacos, úlcera.

INTRODUCTION

Most patients with schizophrenia have at least one chronic comorbid medical condition (Mitchell & Malone, 2006). Metabolic and cardiovascular comorbidity have long been acknowledged (Mitchell & Malone, 2006; Stahl, 2013), however, dermatological disease is also considerably frequent in patients with schizophrenia. Skin conditions such as infection, dermatitis, hyperkeratosis, pilosebaceous disease, androgenic alopecia, xerosis and stasis, are more prevalent in patients with schizophrenia than in those without (Mookhoek, Van De Kerkhof, Hovens, Brouwers, & Loonen, 2010; Wu et al., 2014). Antipsychotic agents are also known to cause adverse cutaneous reactions in approximately 5% of patients (Srebrnik, Hes, & Brenner, 1991), most often exanthematous eruptions, photosensitivity and skin pigmentation (Warnock & Morris, 2002). During the course of type 2 diabetes mellitus (T2DM), cutaneous manifestations can be seen in approximately 30% of patients. Some of these manifestations are related to insulin resistance and appear even before the diagnosis is confirmed (Lima, Illing, Schliemann, & Elsner, 2017; Sanches, Roda, Pimenta, Filipe, & Freitas, 2019). Atypical antipsychotics are linked to a higher risk of cardiometabolic side effects, which include not only T2DM, but also obesity, dyslipidaemia and accelerated cardiovascular disease. Clozapine is among the antipsychotics with the greatest risk (Stahl, 2013).

Patients with schizophrenia have a two to four fold higher risk of T2DM (Annamalai, Kosir, & Tek, 2017) and the antipsychotics used for treatment are an established risk factor for T2DM development. A large-scale systematic review and meta-analysis found a prevalence of 2.9% of T2DM in antipsychotic-naïve patients and 11.3% in patients with severe mental illness medicated with atypical antipsychotics (Vancampfort et al., 2016). It was initially thought that glucose dysregulation resulted from antipsychotic induced weight gain, caused by antagonism of histamine H1 and serotonin 5HT2C, but it is now accepted that glucose metabolism is dysregulated even in the absence of weight gain and changes in lipid metabolism. In vitro and animal studies point towards altered hepatocyte and skeletal muscle cell glucose metabolism, as well as altered insulin secretion and pancreatic beta cell function. Antipsychotic effects on the central nervous system may also influence glucose homeostasis (Grajales, Ferreira, & Valverde Á, 2019). It is yet not definitively established whether antipsychotic polypharmacy compounds the risk for T2DM and metabolic risk (Ijaz et al., 2018).

Most lower extremity ulcers arise from arterial and/or venous pathology, and occur due to a combination of concurrent factors such as trauma, continued friction or pressure and tissue hypoxia (Singer, Tassiopoulos, & Kirsner, 2017). T2DM is a prominent risk factor for the formation and perpetuation of ulcers (Bandyk, 2018; Singer et al., 2017). Atherosclerosis and macro- and microvascular disease due to T2DM could lead to peripheral arterial disease and consequent reduced arterial blood flow. Reduced tissue perfusion results in ischemia and subsequent necrosis and ulceration (Singer et al., 2017). Recurring episodes of ischemia and reperfusion also contribute to tissue injury, as these cycles increase the formation of reactive oxygen species and trigger an inflammatory response (Mervis & Phillips, 2019; Singer et al., 2017). Impaired wound healing due to continued pressure, vascular disease, diabetes associated autonomic and sensory neuropathy, macro- and microvascular dysfunction, hypoxia and chronic inflammation could lead to chronification of ulcers (Baltzis, Eleftheriadou, & Veves, 2014).

With this article, we aim to describe the clinical case of a patient with refractory schizophrenia who developed T2DM and persistent malleolar ulcerations after adding clozapine to her previous antipsychotic regime (long acting haloperidol intramuscular injection), and to explore the possible underlying pathophysiology of these metabolic and cutaneous side effects, which are frequent clinical problems among patients on long term antipsychotic treatment.

CASE DESCRIPTION

A 57-year-old female patient with schizophrenia was admitted involuntarily to our psychiatric hospital due to psychotic decompensation in April 2015. She presented refractory schizophrenia and was prescribed clozapine titrated up to 300mg/day, in addition to the long acting haloperidol intramuscular injection (150mg q21d) she was already on, lorazepam 2.5mg qid and trihexyphenidyl 2mg o.d..

The patient had no known comorbidities and did not smoke or take any substances. Family history included T2DM and hypertension (mother). Baseline laboratory results showed values within the normal range, including fasting glucose (98mg/dL) and lipid profiles (total cholesterol 161 mg/dL, LDL 90mg/dL, HDL cholesterol 60mg/dL, triglycerides 56mg/dL). She had a body mass index of 19.9 kg/m2. Thirteen weeks after initiating therapy with clozapine, blood tests

showed consistent elevation of fasting glucose (up to 140 mg/dL). Metformin 500mg q.d. was initiated and fasting glycaemia returned to consistent normal values after 12 weeks.

Three months after initiating clozapine, she developed non-painful bilateral lateral malleolar ulcers, approximately 1.5 cm in diameter. The ulcers had elevated edges and slough in floor, with no signs of inflammation. Surrounding skin was cool to touch, with reduced pilosity, and skin discoloration; there was no oedema. Patient reported normal sensibility in lower extremities and pedal pulses were bilaterally present. Despite treatment with standard wound dressings, the ulcers did not resolve. She was then presented to the Internal Medicine department, who advised continuation of conservative treatment and no further investigation.

She was treated with standard wound dressings under the diagnosis of pressure ulcer. Later, due to excessive sedation and persistence of ulcers, with sustained psychiatric stabilization, clozapine was reduced and eventually stopped, maintaining long acting injectable haloperidol antipsychotic monotherapy. One month after clozapine discontinuation, in mid-May, the ulcers on both legs began to cicatrize. In April 2016 metformin was suspended and the patient maintained normal glycaemic values, until 2019 when she again developed T2DM (no relationship to changes in medication). Her ulcers did not recur.

DISCUSSION

Patients with schizophrenia have a high prevalence of skin conditions (Wu et al., 2014) and metabolic disturbances. However, to our knowledge, there are no reports of an association between skin ulcers and treatment with clozapine. Multiple factors could have be involved in the formation and perpetuation of these ulcers.

Usually, prolonged pressure elicits a change in body position to prevent shear and friction from affecting underlying capillary beds and contributing to tissue hypoxia and injury(-Mervis & Phillips, 2019). The positive, negative and cognitive symptoms of schizophrenia, a higher pain threshold (possibly as a feature of schizophrenia and/or antinociceptive effects of antipsychotics, especially clozapine) and medication-induced sedation, may drive the development of ulcers by inhibiting this response (Schreiber, Getslev, Backer, Weizman, & Pick, 1999; Seidel et al., 2013; Stubbs et al., 2015; Urban-Kowalczyk, Pigońska, & Śmigielski, 2015; Wu et al., 2014). Decreased mobility due to medication-induced sedation or extrapyramidal effects could also contribute, though this was not a factor in our case as the patient was always mobile.

Our patient had an increase in blood glycaemia upon treatment with clozapine, but normal glucose levels at baseline and after clozapine discontinuation. It is known that T2DM develops over years, with many complications preceding the onset of overt hyperglycaemia (Skyler et al., 2017). Before reaching the diagnostic threshold for T2DM, 20 percent of patients with dysglycaemia alone have an abnormal ankle-brachial index compared with only 7 percent of patients with normal glucose homeostasis (Beks et al., 1995). An observation by a vascular surgery specialist, with measurement of ankle-brachial index to ascertain the presence of peripheral arterial disease would have been important for our clinical case, but was unavailable at the time. The patient did not possess other risk factors for T2DM except for antipsychotic treatment, having been treated for about 20 years. It could be that clozapine simply revealed a process that was already under way, suggesting genetic or epigenetic vulnerability and/or the influence of unrecognized environmental factors (Kolb & Martin, 2017; Skyler et al., 2017; Vaiserman & Lushchak, 2019). It is known that women are more susceptible to the metabolic side effects of atypical antipsychotics than men (Ingimarsson, MacCabe, Haraldsson, Jónsdóttir, & Sigurdsson, 2017).

This is the first report of a patient developing leg ulcers upon treatment with clozapine. Discontinuation of treatment was necessary for symptomatic improvement. The link between skin ulcerations and atypical antipsychotics, such as clozapine, requires further investigation. Metabolic monitoring reveals crucial when treating patients with antipsychotics (Hasan et al., 2013; Taylor, Barnes, & Young, 2018).

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