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trends.denise@gmail.com

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Scopel Hoffmann, Maurício; Mendes Oliveira, Lucas; Rodrigues Lobato, Maria Inês;
Belmonte-de-Abreu, Paulo

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Heat stroke during long-term clozapine treatment: should we be concerned about hot weather?

Heat stroke durante tratamento de longo prazo com clozapina: devemos nos preocupar com o tempo quente?

Maurício Scopel Hoffmann,^{1,2} Lucas Mendes Oliveira,² Maria Inês Rodrigues Lobato,^{1,2,3} Paulo Belmonte-de-Abreu^{1,2,3,4}

Abstract

Objective: To describe the case of a patient with schizophrenia on clozapine treatment who had an episode of heat stroke.

Case description: During a heat wave in January and February 2014, a patient with schizophrenia who was on treatment with clozapine was initially referred for differential diagnose between systemic infection and neuroleptic malignant syndrome, but was finally diagnosed with heat stroke and treated with control of body temperature and hydration.

Comments: This report aims to alert clinicians take this condition into consideration among other differential diagnoses, especially nowadays with the rise in global temperatures, and to highlight the need for accurate diagnosis of clinical events during pharmacological intervention, in order to improve treatment decisions and outcomes.

Keywords: Antipsychotic, heat wave, neuroleptic malignant syndrome, thermoregulation.

Resumo

Objetivo: Descrever o caso de um paciente com esquizofrenia em tratamento com clozapina acometido por um episódio de *heat stroke*.

Descrição do caso: Durante uma onda de calor em janeiro e fevereiro de 2014, um paciente com esquizofrenia em tratamento com clozapina foi inicialmente encaminhado para diagnóstico diferencial de infecção sistêmica e síndrome neuroléptica maligna, tendo obtido o diagnóstico final de *heat stroke*, tratado com controle de temperatura corporal e hidratação.

Comentários: Este relato de caso tem como objetivo alertar os clínicos para este diagnóstico diferencial, que pode surgir com mais frequência à medida que as temperaturas globais continuarem a aumentar, e também destacar a importância da realização de um diagnóstico mais acurado, que possa melhorar as decisões de tratamento e os desfechos clínicos para os pacientes.

Descritores: Antipsicóticos, onda de calor, síndrome neuroléptica maligna, termorregulação.

Introduction

While the effects of clozapine on hematologic, cardiac and liver function have been well studied, very few studies have focused on its effects on body temperature control, despite evidence that neuroleptics have deregulating effects on homeostatic mechanisms of temperature regulation.^{1,2} This may be resulting in a large number of underreported cases, probably with a high rate of hidden morbidity and mortality.² Here we

report a case of clozapine-related heat stroke, in order to raise awareness among psychiatrists and general health professionals who are involved in providing clinical care to people undergoing severe mental illness events, especially during hot seasons.³ It is possible that these events may be being underreported, since neuroleptics have been associated with heat stroke, but only one case report involving clozapine has been published to date.⁴ Neuroleptics have long been known to decrease mean body temperature.⁵ Drugs can alter body temperature by

¹ Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil. ² Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, RS, Brazil. ³ Programa de Esquizofrenia (PRODESQ), HCPA, Porto Alegre, Brazil. ⁴ Departamento de Psiquiatria e Medicina Legal, UFRGS, Porto Alegre, RS, Brazil.

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acting on any of the components of the thermoregulatory system. These components include heat production, heat conservation and heat loss through efferent and/or afferent pathways,^{1,3,6} and actions probably involve mixed effects on the hypothalamic thermoregulatory pathway, and blocking effects over dopamine, serotonin and muscarinic receptors.⁶ Since the incidence of heat-related illnesses increases during heat waves (which are defined as at least 3 consecutive days with air temperatures greater than 32.2 °C) and since global warming is a reality,⁷ it should be expected that there will be a considerable impact on vulnerable populations, such as psychiatric patients,^{2,3} in the coming years.

We report a case of heat stroke seen at a general hospital in southern Brazil during a heat wave in January and February 2014. The patient was on chronic clozapine treatment and was admitted for investigation of a systemic infection or a malignant neuroleptic syndrome (NMS). Our objective is to alert clinicians to this differential diagnosis that may present more frequently as global temperatures continue to rise^{7,8} and also to highlight the importance of conducting precise identification, diagnosis and control of this life-threatening situation in psychiatric patients on continuous neuroleptic use.

Case description

The patient was a 60-year-old male with Caucasian Ashkenazi origins, diagnosed with treatment-resistant schizophrenia, with prominent paranoid symptoms, hallucinations and aggressive-disruptive behavior, with onset at the age of 19, a 22-year record of treatment with clozapine (600 mg/day) and valproate (1,000 mg/day) and no prior adverse events related to these drugs. Since 1991, he had had good control of symptoms and good medical compliance, with monthly visits to the schizophrenia outpatients program (PRODESQ) at a major teaching hospital (Hospital de Clínicas de Porto Alegre) for clinical and laboratory check-ups. The patient presented at a regular and scheduled psychiatric consultation in January 2014 and was stable, with normal blood counts. Three hours later, at home, he called his brother because he was not feeling well and suddenly collapsed to the floor, speaking in a slurred manner, with decreased handgrip strength, and a few minutes later he stopped talking.

He was admitted 1 hour after the event, on the seventh day (39 °C air temperature) of a 27-day heat wave in January and February of 2014, during which environmental temperatures had oscillated between 35 and 42 °C (Figure 1J). At admission he scored 9 points on the Glasgow Coma Scale, exhibited no rigidity or

extrapyramidal symptoms, had an axillary temperature of 41.9 °C, with rales on thoracic auscultation, tachycardia (149 beats per minute), tachypnea (24 inspirations per minute), upper-limit blood pressure (140/90 mmHg), normal oxygen saturation and glucose of 172 mg/dL. He was put on mechanical ventilation, and chest X-ray, electrocardiogram, computerized tomography and lumbar puncture findings were all normal. At the stroke unit he was given intravenous 0.9% NaCl and dantrolene, and NMS, viral meningitis, pneumonia, sepsis or leptospirosis were suspected. Because of these potential diagnoses he was given acyclovir and cefepime on the first day. Valproate and clozapine were stopped. The most important laboratory test results are shown in Figure 1A-D and F-I.

Laboratory tests revealed a low platelet count, elevated creatine phosphokinase activity and an international normalized ratio of 1.27, elevated creatinine, low sodium and normal potassium (Figure 1A-D and 1I). Within the first 24 hours, the patient recovered consciousness and respiratory function, and maintained an axillary temperature below 37.8 °C. Creatine kinase (CK) was markedly increased, and sodium/potassium abnormalities were attributed to previous transient kidney failure. On the sixth day, clozapine was restarted, increasing by 25 mg every two days. On the seventh day, the patient was admitted to an air-conditioned psychiatric ward, and on the twelfth day he was transferred to a standard non-air-conditioned ward, while temperatures during the heat wave increased to around 40 °C. Four days after this, while taking 125mg of clozapine (Figure 1E), the patient again presented with hyperthermia (38-38.9 °C) with increased CK activity (Figure 1A and J). Intravenous hydration was reintroduced and the patient was relocated to an air-conditioned room, which resulted in complete resolution of symptoms and no need to further suspend administration of the antipsychotics. The patient also underwent physiotherapy because of muscle weakness attributed to muscular necrosis. He currently has monthly consultations at the schizophrenia outpatient program and is taking 450 mg of clozapine, and control of psychotic symptoms has been recovered. Both the patient and his legal tutor consented to his case report.

Discussion

To the best of our knowledge, and according to a MEDLINE search with the keywords "heat stroke AND clozapine," this is the second report of heat stroke in a patient with schizophrenia taking clozapine.⁴ Heat stroke is a medical emergency, characterized by a core body temperature above 40 °C and central nervous system

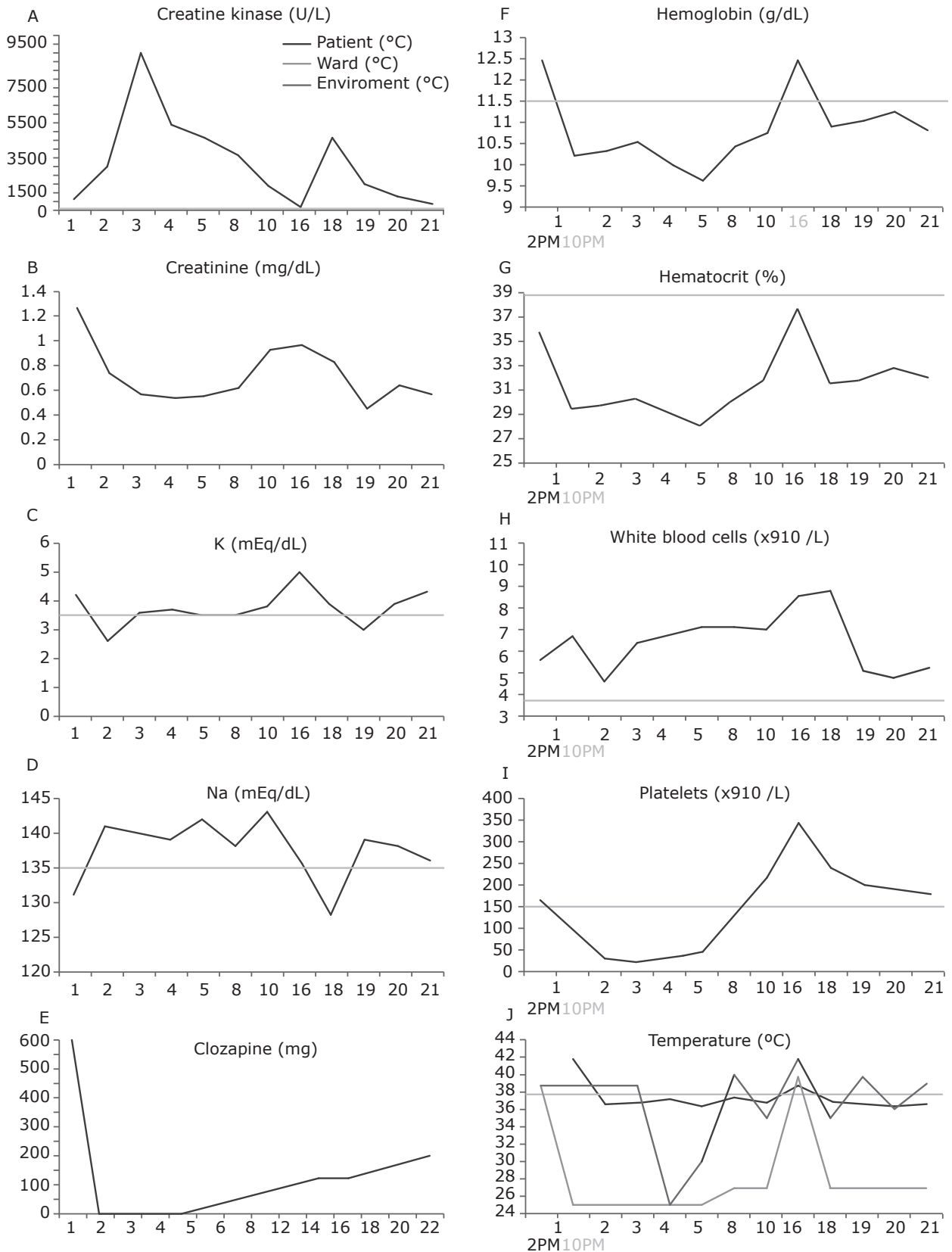


Figure 1 - Panels A-D and F-I show laboratory and clinical findings obtained during the first 21 days of admission. Panel E shows clozapine dosage. Panel J shows maximum temperatures for the patient (axillary temperature), inside the ward and in the outside environment (obtained from <http://www.accuweather.com/pt/br/brazil-weather>). Red lines indicate upper limits in A and J, and lower limits for the other parameters. Numbers in red indicate days with fever or hyperthermia.

dysfunction, resulting from exposure to environmental heat or extreme physical exercise. Core temperatures above this threshold can initiate a cascade, ultimately resulting in multiple organ failure.³ Mortality is around 50% and mental illness, inability to self-care and psychotropic medication use are associated with higher mortality, whereas increased social interaction and exposure to air-conditioned environments are associated with a lower risk of death.^{2,8} Additionally, the present report raises at least two new clinical questions. The first is the issue of early recognition and differentiation from other complications such as NMS and infection. The second is that, although clozapine may interfere in the pathophysiology of heat stroke, it does not necessarily need to be suspended during treatment of the patient.

The incidence of heat stroke has been observed to increase during heat waves, which in turn have been reported to occur more often during the last decade in Europe, America and the Middle East.^{3,8,9} Increasing global temperatures⁷ mean that it is possible that a higher incidence of heat-related illnesses will be observed⁸ and so health care systems and health professionals should be aware of these conditions, to enable faster detection and more rapid treatment, especially in at-risk groups such as psychiatric patients or those being treated with neuroleptics.

Psychiatrists are trained to recognize a series of diseases associated with psychotropic drug administration, such as NMS and serotonin syndrome. Altered mental states, increased CK, increased core body temperature and organ dysfunction can all occur in these syndromes. Lack of rigidity is also a common finding in NMS when it is associated with clozapine use.¹⁰ Despite the similarities between heat stroke and these conditions, treatment options can be markedly different. The main treatment for heat stroke is to transfer internal heat to the external environment, which is achieved by convection cooling (fanning the undressed and wetted patient at a room temperature of 20-22 °C) or by conductive cooling (cooling blankets, application of ice packs, cold water immersion and gastric or peritoneal lavage). Saline infusion can also be given to improve cardiac output due to possible dehydration and also to prevent kidney injury by rhabdomyolysis.³

The patient described here also suffered other clinical manifestations of low fever and increased CK, which might suggest that he was suffering from NMS. However,

the day before, his creatinine levels were approximately 30% higher than usual, demonstrating that the patient could have been experiencing another episode of dehydration associated with high environmental temperatures, leading to increased CK and fever. The clinical decision was to keep the patient on clozapine and isolate the "temperature" factor, based on the main diagnosis of heat stroke. Indeed, the patient did improve and remains on clozapine. This raises questions about whether clozapine played a role in the heat stroke, as has been described previously⁴ and as other antipsychotics have done,^{2,3,8} or whether it is a confounding factor and a neuroleptic that is safe in heat-related illness. Finally, it should be emphasized that clinicians and patients must be aware of vulnerability to environmental heat and concern themselves with the risk of fatal complications such as heat stroke, which can be easily prevented by ensuring adequate temperatures in wards and at home.

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Correspondence:

Maurício S. Hoffmann
Hospital de Clínicas de Porto Alegre
Ramiro Barcelos, 2350/2202
90035-003 - Porto Alegre, RS - Brazil
Tel:/Fax: +55-51-3359-8094
E-mail: mauriciodireito@yahoo.com.br