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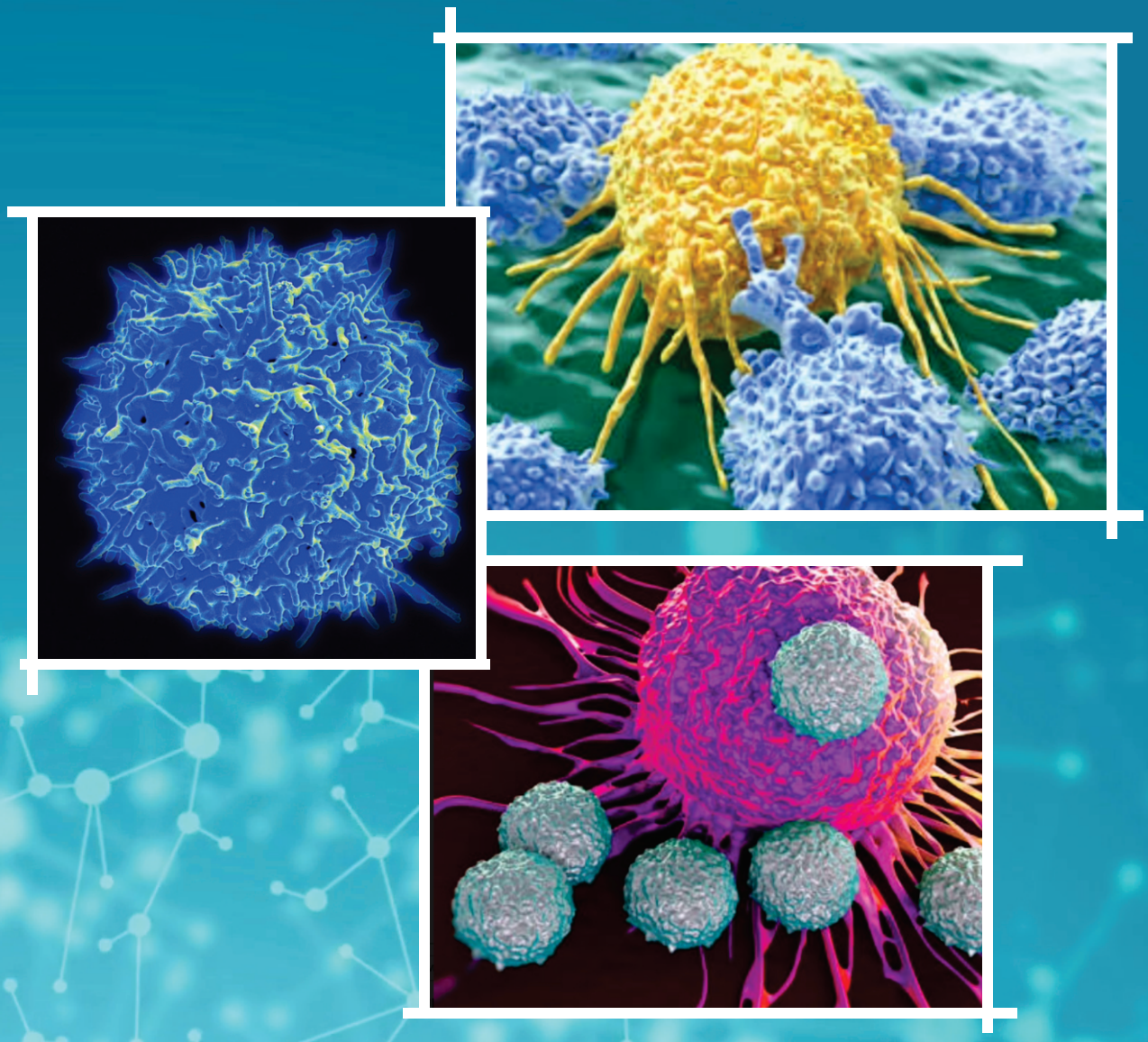

Is the autoimmune diseases prevalence changing? If so, why?

EDITORIAL

IS THE AUTOIMMUNE DISEASES PREVALENCE CHANGING? IF SO, WHY?

Autoimmune diseases (AID) are a varied group of disorders that can target several tissues and organs, and that are associated with an inappropriately activated immune system causing destructive responses against self-antigens. Relatively common autoimmune diseases are pernicious anemia, coeliac disease, Crohn's disease, type 1 diabetes, Graves' disease, Hashimoto's thyroiditis, idiopathic thrombocytopenia purpura, systemic lupus erythematosus, multiple sclerosis, and rheumatoid arthritis.

In the last decades there is some evidence pointing that the incidence of AIDs is raising worldwide paralleling the surge of allergic diseases and cancer while infectious diseases are becoming less frequent. The rapid increase in AID prevalence in developed countries and observations in selected migrant populations, indicate some form of environmental impact driven by the economic status, creating the basis for the hygiene hypothesis. According to Lerner et al, autoimmune neurological diseases has had an yearly mean net increase of 3.7±2.5 %; the gastrointestinal AID of 6.2 ±11.5%, endocrinological of 6.3±4.2% and rheumatological of 7.14±1.5%. This outbreak of AID in industrialized countries has brought into question the role of environmental factors dictated by western lifestyle. Air and water pollution, use of food additives and tobacco exposure are well known examples of possible triggers for AID.

Silica air pollution has been linked to rheumatoid arthritis and scleroderma since a long time, through the well-recognized Caplan and Erasmus syndromes. Caplan syndrome refers to the association of severe rheumatoid arthritis and pneumoconiosis while Erasmus syndrome to scleroderma associated with pneumoconiosis. It is believed that the systemic effects of air pollution exposure are mediated through the induction of pulmonary oxidative stress and inflammation, the mediators from which can spill over into the circulation and influence distant events. Two case-control studies of the relationship between air pollution exposure and the development of type 1 diabetes (T1DM) by Hathout et al found significant associations between ambient air pollution levels and the risk of T1DM, mainly if the disease appears before 5 years of age.

Children with diabetes were also significantly more likely to have been exposed to second-hand smoke than healthy controls. Systemic lupus erythematosus prevalence has been found to be associated with high levels of airborne petroleum products and mercury. Poor air quality has also been linked not only to the appearance of the disease but also to worsening of an already existing autoimmune disease. Oikonen et al. demonstrated a fourfold increase in the risk of multiple sclerosis relapse during periods when the concentration of coarse particulate air pollution was in the highest quartile. Rheumatoid arthritis, systemic lupus erythematosus and spondyloarthritis are rheumatic diseases with worse prognosis in smoking patients. Cigarette smoking affects both the cellmediated and humoral immune responses, inducing the release of TNF-alpha, TNFalpha receptors, interleukin (IL)-1, IL-6, IL-8 and granulocyte-macrophage colonystimulating factor.

Silicone implants and other fillings used in plastic procedures such as paraffin, mineral oil and with other substances as iodide gadital, guyacol have also been linked to increased prevalence of AID such as rheumatoid arthritis, scleroderma and Anca associated vasculitis in genetically predisposed individuals. Siliconosis not always refers to a fully characterized ATD but also to a set of ill-defined signs and symptoms such as arthralgias, chronic fatigue, cognitive dysfunction that appears in these patients.

Animal studies have shown significant elevations of various auto-antibodies in experimental mice that spontaneously developed autoimmune disease after silicone implantation, including anti-dsDNA antibodies and rheumatoid factor. In siliconosis, symptoms may improve in about half of patients that remove the silicone implant. Recently, siliconosis was incorporated into a newly defined syndrome entitled 'ASIA' or Autoimmune (Autoinflammatory) Syndrome Induced by Adjuvants described by S. Yehuda et al. ASIA or Schoenfeld Syndrome encompasses several enigmatic conditions such as post-vaccination phenomena, Gulf War syndrome, macrophagic myofasciitis syndrome and siliconosis, which all display similar manifestations.

ATD following vaccination has been assigned to the presence of adjuvants

(e.g.aluminium) . Adjuvants' are able to chronically stimulate the immune system and mainly the innate immune system (for example, toll-like receptors). They protect the antigens from being degraded and allow them to have a better and long lasting exposure to the antigen presenting cells. There are well-described data alluding to adjuvants per se as agents that can induce not only autoimmunity (for example, the emergence of a variety of autoantibodies and hypergammaglobulinemia), but also, in a few cases, well defined autoimmune diseases. High incidence of Guillain-Barre´ syndrome following the swine-flu vaccination programme in North America in 1976–1977, have been documented. However, vaccines are of the most significant tools in preventive medicine nowadays. Eradication of infectious diseases becomes possible through vaccination programs, so this data should not be interpreted without care. ATD following vaccination happens in a minority of exposed people that may have a genetic predisposition.

The influence of chemical exposures in the AID prevalence is an area of growing interest that deserves to be better studied with rigorous methodology to truly access prevalence, individual risk factors, morbidity, mortality, as well as its economic impact. Although it is lacking strong evidence in this type of association it is always good to remember that where there is smoke there must be fire…. or, maybe, an autoimmune disease.

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Thelma L Skare.
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ORIGINAL ARTICLE
TOPICS IN MEDICAL CLINIC
CATARACT IN PATIENTS WITH AND WITHOUT OSTEOPOROSIS
CATARATA EM PACIENTES COM E SEM OSTEOPOROSE

FLAVIA ENCARNAÇÃO LONGO[1]
LUIS FELIPE TAKADA[1]
MARCELO L. GEHLEN[2]
THELMA L SKARE[3]

Descritores: Osteoporose; Catarata; Facectomia
Keywords: Osteoporosis; Cataract; Facectomy

Resumo

A osteoporose caracteriza–se por uma alteração da massa óssea que culmina com um aumento no risco de fraturas. Já a catarata é caracterizada por qualquer opacidade do cristalino; é uma das principais causas de cegueira na população idosa. Alguns estudos relatam a importância do metabolismo do cálcio no desenvolvimento da catarata e também a osteoporose. **Objetivos:** Verificar a prevalência de catarata em pacientes com e sem osteoporose. Avaliar a prevalência de catarata quanto à idade, Índice de massa corpórea, raça, sexo e grau de osteoporose dos pacientes. **Métodos:** Este foi um estudo transversal, que contou com a participação de 102 pacientes. Destes, 82 tinham catarata e 20 pacientes sem. Foi considerada uma amostra de conveniência não probabilística de pacientes ambulatoriais do Serviço de reumatologia do Hospital Universitário Evangélico de Curitiba. Compararam-se resultados de densitometria óssea pelo DEXA, raça, exposição a luz solar, idade e índice de massa corporal (IMC) entre os dois grupos. **Resultados:** A mediana de IMC dos pacientes com catarata foi menor (26,6 Kg/m2) do que nos sem (29,3Kg/m2; P=0,03). Pacientes mais idosos tiveram maior prevalência de catarata quando comparados a pacientes mais jovens (P=0,01). Não se observou aumento de prevalencia de catarata de acordo com massa óssea medida pelo DEXA em g/cm2, T escore e Z escore (todos p=ns) **Conclusão:** A prevalência de catarata foi maior em pacientes com idade maior e com índice de massa corporal menor. Não se encontrou significância estatística entre presença de catarata e raça, sexo e grau de osteoporose dos pacientes. **Endocrinol diabetes clin exp 2018 2021 - 2024.**

Abstract

Osteoporosis is characterized by a change in bone mass that culminates with an increased risk of fractures. Cataract is characterized by any opacity of the lens,and its one of the main causes of blidness in the elderly. Some studies report the importance of calcium metabolismo in the development of cataracts and also osteoporosis. Objectives: To verify the prevalence of cataract in patients with and without osteoporosis. To evaluate the prevalence of catraract in terms of age, body mass index, race, sex, and osteoporosis level of the patients. Methods: This was a cross-sectional study involving 102 patients. Of these, 82 had cataracts and 20 patients were without it. It was considered a non-probabilistic convenience sample of outpatients from the Rheumatology Service of the Hospital Universitário Evangélico de Curitiba. Results of bone densitometry by DEXA, race, exposure to sunlight, age and body mass index (BMI) were compared between the two groups. Results: The median BMI of the patients with cataract was lower (26.6 Kg / m2) than in those without it (29.3 kg / m2; P = 0.03). Older patients had a higher prevalence of cataract when compared to younger patients (P = 0.01). No increase in the prevalence of cataract according to bone mass measured by DEXA in g / cm2, T score and Z score was seen (all p = ns). Conclusion: The prevalence of cataract was higher in patients of greater age and with a lower body mass index. No statistical significance was found between the presence of cataract and race, sex and osteoporosis degree of the patients. **Endocrinol diabetes clin exp 2018 2021 - 2024.**

INTRODUCTION

Osteoporosis (OP) is a complex disorder of multifactorial, systemic and progressive origin. It is characterized by a deficit in bone mass and wear of microarchitecture that culminates with an increased risk of bone fractures (1). OP is in the group of chronic degenerative diseases that had increased incidence in the twentieth century after several structural changes in society leading to a drop in mortality and increase in life expectancy (1).

Decreased bone mineral density (BMD) with age is a universal physiological phenomenon, affecting all races and cultures, being non pathological in most of the cases. However, the decrease in BMD favors the development of osteoporosis (2), which can be defined, according to the World Health Organization (WHO), as a metabolic disease that is characterized by the decrease and deterioration of the microarchitecture of bone tissue, with consequent increase in bone fragility and fracture susceptibility (3). Calcium metabolism imbalance may play a role in its appearence (4,5).

Cataracts affect 10% of the world population, with higher prevalence in older individuals (6). It affects three in four individuals older than seventy and can lead to a total vision loss. For this reason it is considered a serious public health problem in developing countries (7). The pathophysiological mechanism of cataract is not fully elucidated, but it is known that theere is a protein aggregates that disperse light rays and decrease the lens transparency. There are also other changes in proteins that determine a yellow or brown coloration. Other findings may be: vesicles between the lens fibers or migration and expressive increase of epithelial cells (8). Cataract is favored by advanced age, use of corticosteroids, myopia, UV radiation, diabetes mellitus, smoking, traumas, use of antipsychotics, or it can be secondary to other pathologies such as uveitis, tumors, acute glaucoma and degenerative eye diseases (7,8). Cataract surgery, also called a facectomy, is the only way to

[1] Curso de Medicina da Faculdadade Evangélica do Paraná (FEPAR)
[2]Disciplina de Oftalmologia da FEPAR
[3]Disciplina de Reumatologia da FEPAR.
E mail: tskare@onda.com.br

cure the disease (9).

Calcium seems to be important in the development of cataracts, since calcium levels control crystalline homeostasis (10). Therefore, both cataract and osteoporosis may be associated with the breakdown of calcium homeostasis (11). International studies have shown a relationship between cataract and osteoporosis. However, in Brazil we do not have any studies related to the subject.

In this study we aimed to assess the prevalence of facectomy by cataract regarding the age, BMI, race, sex, and degree of osteoporosis of patients.

MATERIAL AND METHODS

This is a cross-sectional observational study of 102 patients from the outpatient Rheumatology clinic at Hospital Universitário Evangélico de Curitiba (HUEC). To be included they have to sign a free and informed consent form, be older than 40 years of age and to have results of bone densitometry in their charts done at least six months before the inclusion. Individuals who used or had used oral glucocorticoids for more than 3 months or eyedrops containing corticosteroids for any amount of time, those who had any ocular inflammatory process (uveitis, scleritis etc.), patients with renal insufficiency, inflammatory bowel diseases, thyroid disease or rheumatoid arthritis were excluded. The patients' identity was preserved in compliance with Resolution 466/12 of the Brazilian National Health Council.

Data collection was carried out through questionnaires elaborated by the authors involving: patients' age, sex, race, housing area (rural or urban), occupational sun exposure, hours of sun exposure per day, smoking (packs-year), alcohol intake, weight and height for calculation of body mass index (BMI), presence of menopause, diabetes, results of bone densitometry, history of cataract and facectomy.

The data obtained was analyzed by frequency and contingency tables. For association calculations, Chi-square or Fisher (nominal data) and Mann Whitney or unpaired Student T tests (for numerical data) will be performed using Graph Pad Prism software version 5.0. Significance adopted of 5%.

RESULTS

A total of 102 patients were included: 92 were women and 10 men, all of whom fulfilled the criteria for inclusion in the study. The age of patients admitted ranged from 46 to 94 years (mean of 69.2 ± 8.2 years), with a predominance of the Caucasian race (92.2%). Regarding sun exposure, 37 patients reported daily exposure to solar radiation (36.3%) that ranged from 2 to 15 hours per day with a mean solar exposure of 8.6 ± 3.2 hours/day. Of the patients analyzed, 32 were exposed to smoking (31.3%), with a smoking load of 0.2 to 60 packs/year (mean of 17.8 ± 12.5). The BMI ranged from 19.84 to 45.3 kg/m2 with a median of 26.6 kg/m2 (IQR=24.4-29.3 kg/m2). Of the 102 patients analyzed, 82 (80.4%) reported having cataract and 49 had undergone cataract correction surgery until the time of the study. All the studied women had already had menopause. In this group 43 (42.2%) had osteoporosis; 47 (46.1%) had osteopenia and 12 (11.8%) had normal densitometry.

The comparison of epídemiological data between patients with and without cataract is on **Table 1**.

Table 1: Comparison of edpidemiological data in patients with and without cataract.

	With cataract n=82	Whithout cataract N=20	P
Gender	Male -8 Female -74	Male- 2 Female -18	1.00
Age (years)	46.0-94.0 Mean 70.2±8.3	54-80 Mean 65.3±7.0	0.01
Ethnic background	Eurodescendants –76/82 -92.6% Afro- 6/82- 7.3%	Eurodescendants =18/20 –90% Afro= 2/20 - 10%	0.65
Living Area	Rural –21/82- 25.6% Urbaa-61/82- 74.3%	Rural –7/20 – 35% Urban-13/20-65%	0.39
Solar exposure (yes/No)	27/82- 32.9%	10/20-50%	0.15
Hours of solar exposure	2.0-15.0 Mean 8.5±3.33	3.0-14.0 Mean 8.7±3.1	0.93
Tobacco exposure	Yes - 8/82 -9.7% No-57/82 – 69.5% Ex-17/82-20.7%	Yes -3/20 – 15% No-13/20 – 65% Ex-4/20 – 20%	0.7
Smoking load	0.2-60.0 Mean 17.6±13.09	7.0-40.0 Mean 18.7±11.3	0.83
BMI – Kg/m2	19.84-45.3 Median 26.2 (24.4-28.3)	20.0-38.05 Median 29.3 (25.6-32.3)	0.03

The analyzis of DEXA results according to presence of cataract is on Table 2.

Table 2: Comparison of DEXA values in patietns with and whithout cataract

	With cataract N=82	Without cataract N=20	
Osteoporosis (n)	35/82 – 51.2%	8/20 – 40%	0.82
Osteopenia (n)	38/82 – 56.0%	9/20 – 40%	0.91
Hip			
Density (g/cm2)	0.427-1.155 Mean =0.750±0.147	0.523-0.918 Mean= 0.755±9.147	0.89
T score	-3.9 - 2.4 Mean= -1.49±1.322	-3.30 - 0.90 Mean= -1.41±1.22	0.81
Z score	-2.6 -5.40 Mean -0.40 (-1.50 -0.30)	-2.0 -1.7 Mean -0.60 (-0.95 -0.25)	0.81
Spine			
Density (g/cm2)	0.497 - 1.357 Mean 0.818±0.149	0.605-1.114 Mean= 0.833±0.143	0.69
T score	-5.0 -2.80 Mean= -1.80 ±1.45	-4.0 - 0.80 Mean= -1.80±1.46	1.00
Z score	-3.40 - 5.00 Mean= -0.45±1.56	-3.30- 3.40 Mean= -0.50±1.71	0.91

DISCUSSION

In the present study, a p value <0.05 was found for the variables of age and BMI in the development of cataract.The variables gender, race, housing area, sun exposure, smoking, osteoporosis, osteopenia and densitometry results did not provide statistical significance. The present study was conducted to verify the relationship between cataract and osteoporosis that are diseases of great prevalence in our environment. If this had been confirmed, it would be of great importance since it would be possible to guide both health professionals and the general population of this association of both diseases, and to start a screening for one or the other as soon as possible in order to avoid and prevent complications of these pathologies. One of the complications of cataracts is blindness, which according to WHO reaches 45 million people, 40% of which are due to cataracts (9). With respect to osteoporosis we have the important increase in the question of fractures in a population of more advanced age. (1)

The presentr work has 2 limitations. The first one is that the number of patients in the sample which was quite small. The second occurred due to technical limitations that did not allow us to take a slit lamp examination in all patients, which would allow us to obtain a more reliable result regarding the prevalence of cataract. Therefore, only the data of facectomy and previous diagnosis of cataract were used, based only on questionnaires applied to the patients.

Our sample shows to be composed mostly of women with a more advanced age (around 69.2 years). These factors may in themselves be related to the fact that the data are collected in a rheumatology outpatient clinic. In a study conducted in Goiás with 7954 patients by OLIVEIRA et al. (2011) (12) about half of the patients diagnosed with cataract were older than 70 years and 36.4% were between 60 and 69 years old. Despite this, in our study when the comparison of the groups with and without cataract, gender did not have any significance. Regarding the age we observed significance with p of 0.01, showing that, the higher the patient's age, the greater the incidence of cataract. This data is in agreement with those found by FERRAZ et al. (2002) and OLIVEIRA et al. (12).

Regarding race, we did not find statistically significant differences in the incidence of cataract. Our sample consisted mainly of people of European descent (92.1%) and a minority of Afrodescendants. This may be due to the fact that Afro-descendants have a lower prevalence of osteoporosis when compared to Caucasians. However, between these 2 groups (with and without cataract) we observed that the prevalence of cataract in the population of European and Afrodescendant descent was practically the same, thus not demonstrating significance. One of the limitations in this analysis may be due to a relatively small sample of different ethnic groups.

The housing area of the survey participants was predominantly urbanized with about 74% of the participants living in urban areas. This factor is probably related to the location of the research site that is in an outpatient clinic in the urban area, and in addition, most of the population follow the urban trend of a globalized world. However, this result did not show statistical significance reaching a value of p= 0.39.

According to OLIVEIRA et al., (12) people with habits related to intense sun exposure are twice as likely to develop cataracts, especially cortical ones. Of the 102 patients in the sample 32 reported having some relevant exposure to sunlight, mainly related to work activities. However, contrary to what is found in the literature, of the total number of patients with cataract (82 patients), only 27 had this exposure related to sunlight, about 32.9%. Regarding the patients without cataract (20 patients), half had sun exposure and nevertheless did not develop cataracts. Such a result can be given by a small sample of patients without cataract, The amount of hours of exposure to sunlight was equal in the 2 groups, also not showing significance. The sun exposure group may have had a number of hours of exposure below that necessary to cause the cataract to appear.

Smoking according to Arieta (13) is related to the risk of developing cataracts mainly of the nuclear and posterior subcapsular type. , Smok8ing is also associated with osteoporosis since it implies early menopause and loss of estrogen on the bone. (1,2) In the present study, the exposure to smoking and

the smoking load ended up not being statistically significant. Most of our sample ended up being composed of non-smokers and patients with cataract, leaving only a small part of patients without cataract and non-smokers, which detracted from the statistical analysis.

According to DEFAY et al., (14) all studies focusing on age dependent ocular diseases have demonstrated a higher prevalence of cataract in older women. However, these authors concluded in their study with 2584 patients that hormone replacement therapy had no relation to cataract. However, HALES et al. (15) demonstrated some protection in the development of cataract by estrogen. The same is true of bone mass. (1,2) About 92 women participated, 74 had cataracts and 18 had no cataracts, but all were already in menopause.

A very interesting finding of the present study was the jnverse relationship between BMI and cataract. The median overall body mass index was 26.6 kg / m2 which indicates pre-obesity or overweight (25-29.9 kg / m2) in the sample patients according to the Brazilian Obesity Directive (16). In the meta-analysis of PAN and LIN (17) including 6 prospective studies with a total of 163,013 patients, obesity was a factor associated with increased risk of nuclear, cortical and posterior subcapsular cataract and overweight was associated with an increased risk of cataracts of the posterior subcapsular type. They conclude that obesity may be an independent risk factor for age-related cataract. According to this meta-analysis (17) there are several explanations for the association between cataract and the increase in body fat index. First would be related to the increase of leptin (cytokine) expressed by adipocytes mainly that would increase the accumulation of reactive oxygen species leading to an increase of the oxidative stress that is already known to be well involved in the process. A second explanation would be due to an increase in pro-inflammatory substances such as C-reactive protein and cytokines that would be elevated due to obesity. Neverthless , in the study of TAI et al., (2009) performed in Singapore with 3000 patients using slit lamp examination, it was found that obesity shows an association inconsistent with cataract and that causality could not be established. The present study found a different result from the other authors, since the group of patients with cataract had a median of 26.2 kg / m2 while the group without cataract had a median of 29.3 kg / m2.

With regard to the analysis of the densitometry that sought to relate the results of this, as well as the diagnoses of osteoporosis and osteopenia with the development of the cataract were demonstrated with no significance. These results for densitometry demonstrate the opposite of that found by NEMET et al., (11) who carried out a database search with a sample of 38,952 patients and concludes that osteoporosis is associated with the presence of cataract. Our small sample size may be responsible for the discrepancy in the results.

CONCLUSION

We conclude that, in our sampole, the presence or not of osteoporosis did not imply an increase in the prevalence of cataract when compared with the normal population. The prevalence of cataract was higher in patients with greater age and lower BMI.

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Correspondance to: Thelma L Skare
Travessa Luis Leitner, 50. Curitiba PR

CASE REPORT
AN ATYPICAL CASE OF CRANIOPHARYNGIOMA AND ACROMEGALY
UM CASO ATÍPICO DE CRANIOFARINGIOMA E ACROMEGALIA

LUÍS JESUÍNO DE OLIVEIRA ANDRADE[1]
GABRIELA CORREIA MATOS DE OLIVEIRA[2]
CLEBER CÂNDIDO SILVA JÚNIOR[3]

Keywords: Craniopharyngioma; Acromegaly; Growth hormone
Descritores: Craniofaringioma; Acromegalia; Hormônio do crescimento.

Resumo

Craniofaringiomas são tumores benignos raros, que ocorrem mais comumente no interior da glândula pituitária ou acima dela e derivam de restos de tecido embrionário a partir do qual deriva a glândula pituitária. Relatamos um caso raro de craniofaringioma associado com acromegalia com achados atípicos à ressonância magnética (MRI). As imagens do tumor à MRI de crânio demonstrou alta intensidade de sinal em imagens ponderadas em T1 e T2, demonstrando extensa lesão heterogênea, sem calcificação e ocupando a área selar e supra-selar. Além disso, o paciente apresentava características clássicas de acromegalia e elevados níveis séricos de IGF1 e níveis não suprimidos de hormônio do crescimento após teste de tolerância à glucose oral. **Endocrinol diabetes clin exp 2018 2025 - 2027.**

Abstract

Craniopharyngiomas are rare benign tumors, which most commonly occur within the pituitary gland or above it, and derive from remnants of the embryonic tissue from which the pituitary gland is derived. We report a rare case of craniopharyngioma associated with acromegaly and atypical magnetic resonance imaging (MRI) findings. The tumor of the patient in the MRI head images demonstrated a predominantly high signal intensity on all T1-weighted, proton-weighted and T2-weighted images, showing heterogeneously space-occupying extensive lesion without calcification within the sellar and suprasellar areas. In addition, the patient presented classical features of acromegaly, and elevated serum IGF1 levels, and unsuppressed growth hormone levels after an oral glucose tolerance test. **Endocrinol diabetes clin exp 2018 2025 -2027.**

INTRODUCTION

Craniopharyngiomas are epithelial tumors that originate from the embryonic remains of squamous cells through of the craniopharyngeal duct. Has prevalence 2% to 5% of all primary intracranial tumors and your incidence around 0.13 to 2 cases per 100.000 person-years (1). Magnetic resonance imaging (MRI) with and without contrast, accurately demonstrates the extent of the tumor and, in particular, its involvement with the hypothalamus. It is the investigation of choice to plan the surgical approach. Angio-resonance is useful to not only delineate the vascular path, but also to help differentiate a tumor from a possible vascular malformation (2). Histologically presents tumor cells small with an epithelial appearance. Numerous micro cystic spaces are formed. Other findings include hyalinised calcified structures, collagen, fibroblasts, foreign body giant cells and occasionally cholesterol clefts (3). We report a rare case of craniopharyngioma associated with acromegaly and atypical MRI findings.

CASE REPORT

A 42-year-old man presenting with classical features of acromegaly, coarse facial features, enlarged hands and feet, and complete loss of vision (Figure 1). He had elevated serum IGF1 levels and unsuppressed growth hormone (GH) levels after an oral glucose tolerance test. MRI revealed a heterogeneously space-occupying extensive lesion without calcification within the sellar and suprasellar areas. (Figure 2A, 2B). A left fronto-temporal craniotomy and a sub-frontal approach were followed. Decompression of the optic nerves/chiasm was not achieved, and complete removal was not possible due to the adherence of tumor to the left sellar/cavernous region. Histology revealed overall features were consistent with craniopharyngioma (Figure 3A).

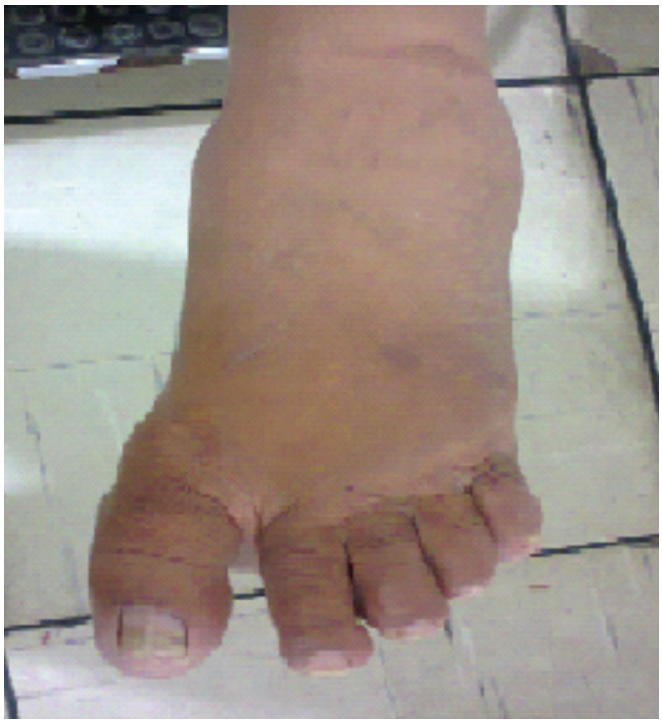


Figure 1. The patient exhibited the typical features of acromegaly.

[1]Colegiado de Medicina – Universidade Estadual de Santa Cruz – Ilhéus, Bahia, Brazil.
[2]Faculdade de Medicina Unime - Bahia, Brazil.
[3]Serviço de Neurocirurgia - Santa Casa de Itabuna, Bahia, Brazil.
E-mail:luis_jesuino@yahoo.com.br

Figure 2. Coronal (A) and sagittal (B) MRI head images showing heterogeneously space-occupying extensive lesion without calcification within the sellar and suprasellar areas.

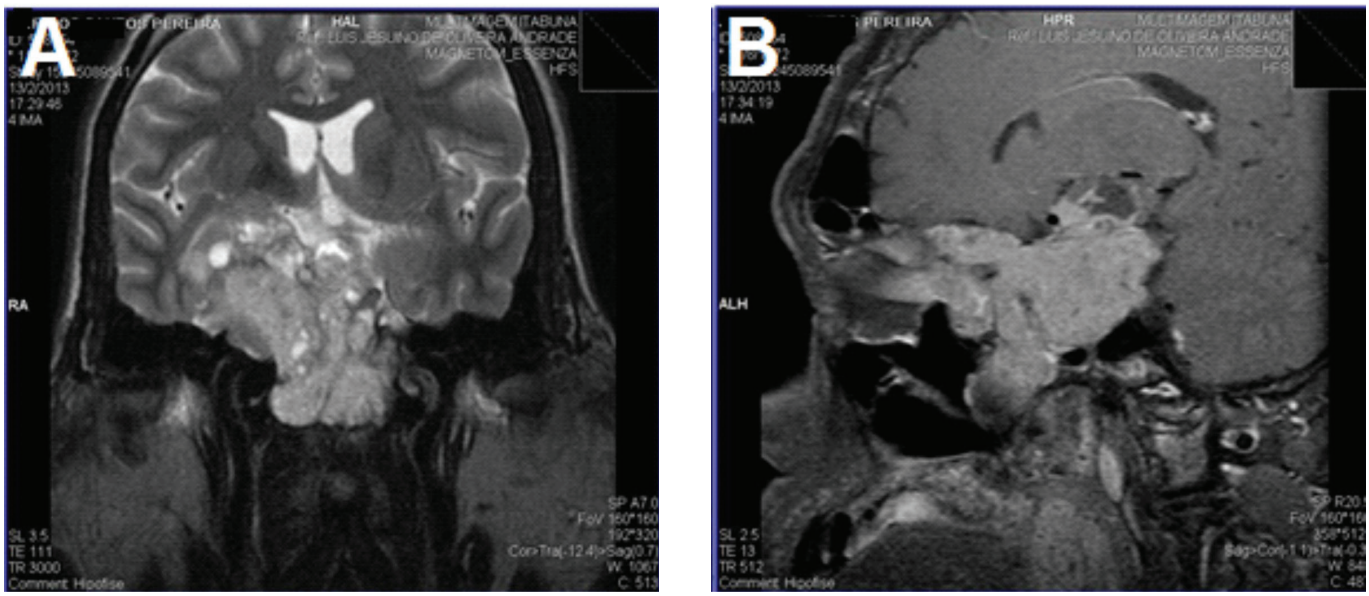
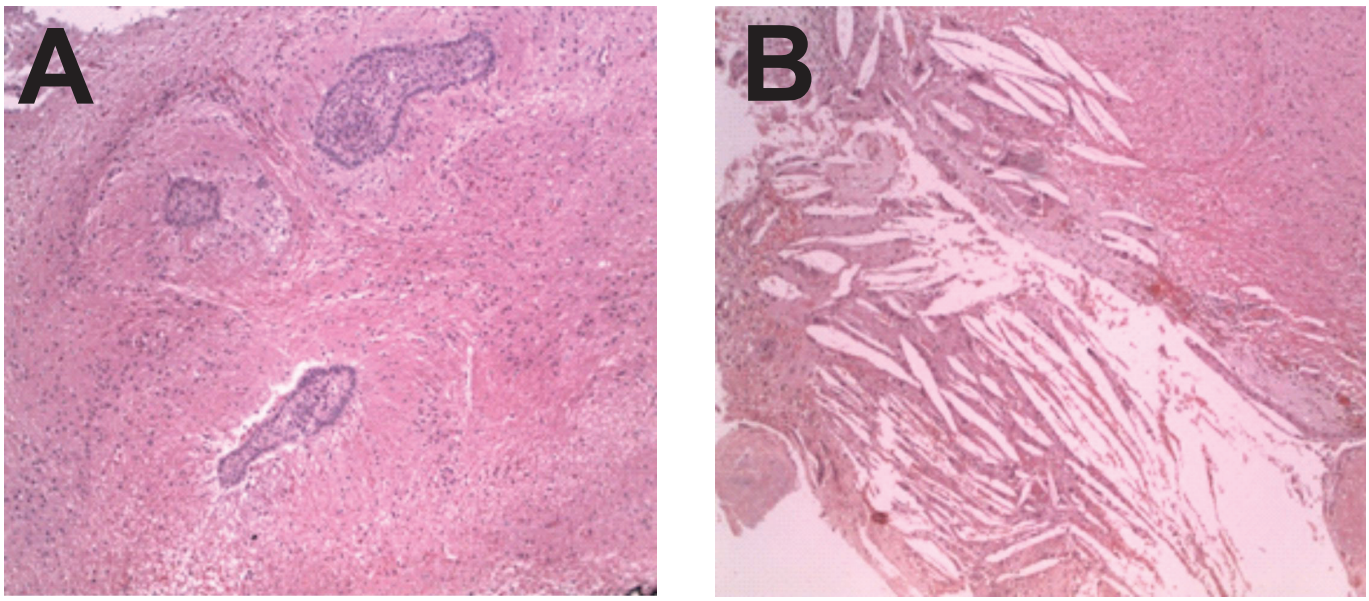


Figure 3 A. Typical adamantinomatous epithelium with peripheral palisading of a single cell layer bordering clusters of loose stellate cells. **B**. Inflammatory infiltrate involving cholesterol crystals.



DISCUSSION

The association between craniopharyngiomas and acromegaly is very rare. Normally suppressed endocrine function, for example hypothyroidism, orthostatic hypotension, short stature, diabetes insipidus, impotence and amenorrhoea, but there can be an exaggeration of endocrine function, for example precocious puberty in children and obesity in adults (4). Only one case of association between craniopharyngioma and GH secreting pituitary adenoma was reported in the literature (5).

The reported case, it is a craniopharyngioma with a probable second primary tumor of pituitary GH secreting in a patient with acromegaly. The surgical approach not captured pituitary tissue of probable adenoma GH secreting. Both pituitary gland and the craniopharyngioma have the same embryonic origin, deriving from the Rathke pouch (6). There are reports of association beta-catenin gene in the initiation and subsequent growth of craniopharyngiomas and pituitary adenomas (7). Adenomas pituitary usually secrete prolactin probably due to compression with resultant lactotroph hyperplasia (8). Hormone deficiency syndromes are present in the craniopharyngioma, except serum prolactin levels (9). In this case, all pituitary hormones analyzed were normal, except for GH and IGF-1 levels.

CONCLUSION

In summary, we report a rare case of a patient with uncontrolled acromegaly due to a sellar and suprasellar craniopharyngioma.

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Correspondence to: Luis Jesuíno de Oliveira Andrade
Rua Nações Unidas, 511 – Centro.
CEP: 45.600-670 Itabuna – Bahia – Brazil.

CASE REPORT AND LITERATURE REVIEW
CASE STUDY: HYPOFISARY MUCORMYCOSIS DIAGNOSED AFTER MACROADENOMA RESECTION

RELATO DE CASO: MUCORMICOSE HIPOFISÁRIA DIAGNOSTICADA APÓS RESSECÇÃO DE MACROADENOMA

GUILHERME GABARDO ADRIANO*

Keywords: Mucormycosis /diagnosis; Mucormycosis/treatment; Pituitary macroadenoma; Fungi infections
Descritores: Mucormicose/diagnóstico; Mucormicose/tratamento; Macroadenoma hipofisário; Infecções fúngicas

Resumo

Mucormycosis is a potentially fatal fungal disease that can affect immunocompetent as well as immunocompromised patients. This infection typically occurs in patients with diabetic ketoacidosis and patients in treatment with chemotherapy for hematologic neoplasia among other conditions. Diagnosis of mucormycosis is supported by clinical manifestations as well as mycological and histopathological analysis. High rates of morbidity have been linked to the delay of diagnosis, reinforcing the need for early diagnosis. The present case report is about a patient diagnosed with mucormycosis based on anatomopathological analysis of pituitary's material after macroadenoma resection. **Endocrinol diabetes clin exp 2018 2028 -2032.**

Abstract

A mucormicose é uma doença fúngica potencialmente fatal que pode acometer tanto imunocompetentes como imunocomprometidos. Geralmente ocorre em pacientes com cetoacidose diabética, em quimioterapia para neoplasias hematológicas ou não, entre outras condições. O diagnóstico é apoiado nas manifestações clínicas e na análise micológica e histopatológica. A demora diagnóstica justifica a alta morbidade da doença, sendo fundamental o início precoce do tratamento. O presente relato de caso é sobre um paciente com diagnóstico de mucormicose por análise anatomopatológica de material hipofisário após ressecção de macroadenoma. **Endocrinol diabetes clin exp 2018 2028 -2032.**

INTRODUCTION

Mucormycosis, previously called zygomycosis, refers to several different diseases caused by infection with fungi in the order Mucorales. Rhizopus species are the most common causative organisms. In descending order, the other genera with mucormycosis-causing species include *Mucor, Cunninghamella, Apophysomyces, Lichtheimia (formerly Absidia), Saksenaea, Rhizomucor*, and other species. Most mucormycosis infections are life-threatening, and risk factors such as diabetic ketoacidosis and neutropenia are present in most cases. Severe infection of the facial sinuses, which may extend into the brain, is the most common presentation. Pulmonary, cutaneous, and gastrointestinal (GI) infections are also recognized. Successful mucormycosis treatment requires correction of the underlying risk factor(s), antifungal therapy (traditionally with a polyene), and aggressive surgery (1, 2). We here report a case of a diabetic male patient with pituitary mucormycosis identified after macroadenoma resection.

CASE REPORT

J.J.N., a 55-years-old male, with type 2 diabetes and hypertension, currently using gliclazide 30 mg and losartan 50 mg once a day. He was admitted to Hospital Universitário Evangélico Curitiba PR Brazil (HUEC) by the neurosurgery department and had a history of 3 days of fever (maximum temperature of 102.2ºF), decrease of general health status and hyporexia. There were no complaints of cough, odynophagia, otalgia, no alterations of genitourinary and gastrointestinal habitus. At admission patient presented hypotension (70/40 mmHg) with partial response after volemic reposition.

Patient's past history reported 15 days of intermittent migraine on right frontal lobe, that was treated by administration of commonly used analgesic drugs. There were no complaints of nauseas or vomits associated with the presence of intermittent diplopia, mainly detected after horizontal movement of the eye to the left, which started 7 days after the primary symptoms, that was recovered progressively on the following days. Computed tomography (CT) of the head detected an increased diameter of sella turcica and sella turcica's MRI demonstrated a large heterogenic expansive lesion centered in the sellar region that also accomplished a large area of sphenoid sinuses, that apparently dislocated the pituitary gland posterior-superior suggesting a hemorrhagic pituitary macroadenoma with extension into sphenoid sinus (figure 1-3). Patient was then submitted to a microsurgery for resection of the expansive sellar lesion with intralesional hemorrhage and compression of optic chiasma. After surgery, patient developed central diabetes insipidus that was reverted with desmopressin used daily and pan-hypopituitarism (TSH 0,04; FSH 0,6; LH 0,25, PRL < 0,6) – measured while hospitalization at HUEC that showed signs of improvement after administration of hydrocortisone IV and levotiroxine.

Anatomopathological definitive report of pituitary chirurgical piece showed hyalohyphomycosis, suggesting mucormycosis (figure 3-5) and skull CT evidenced the presence of material on maxillary sinus (on the right), pedunculate filled with liquid (figure 7), material at sphenoidal sinus, ethmoid cells and frontal sinus. Patient was then submitted to a biopsy of maxillary sinus by the otorhinolaryngology team that confirmed mucormycosis. Patient still under treatment at Day Hospital taking amphotericin B lipid complex, after administrating amphotericin B deoxycholate. During the period of hospitalization, patient presented glycemic lability, hypoglycemic periods that needed high doses of insulin and hypoglycemic periods that improved after disruption of insulin therapy. When patient was released from HUEC he was hemodynamic stable, controlled blood glucose and no signs of fever.

* Serviço de Endocrinologia e Diabetes, Hospital Universitário Evangélico de Curitiba, Paraná, Brazil.
E-mail: guigabardo@hotmail.com

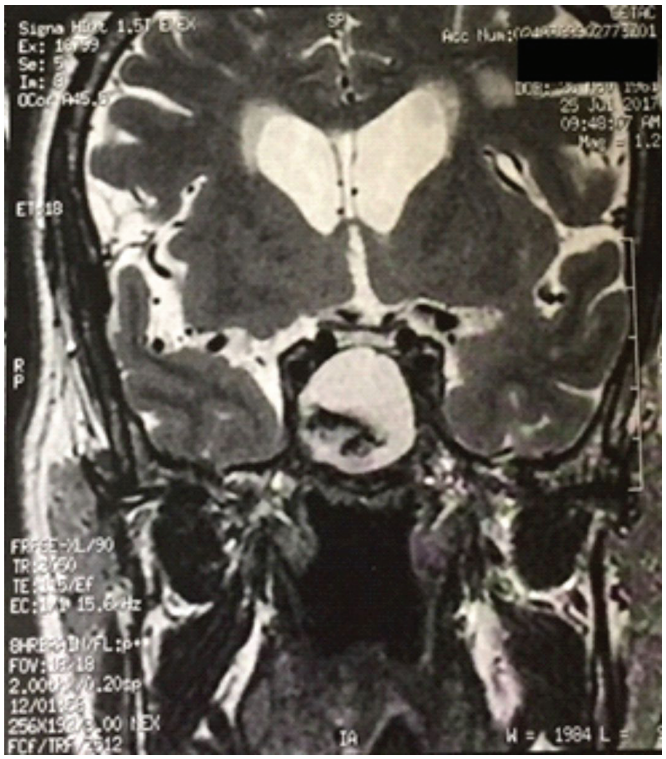

Figure 1. Heterogeneous expansive lesion at sellar region

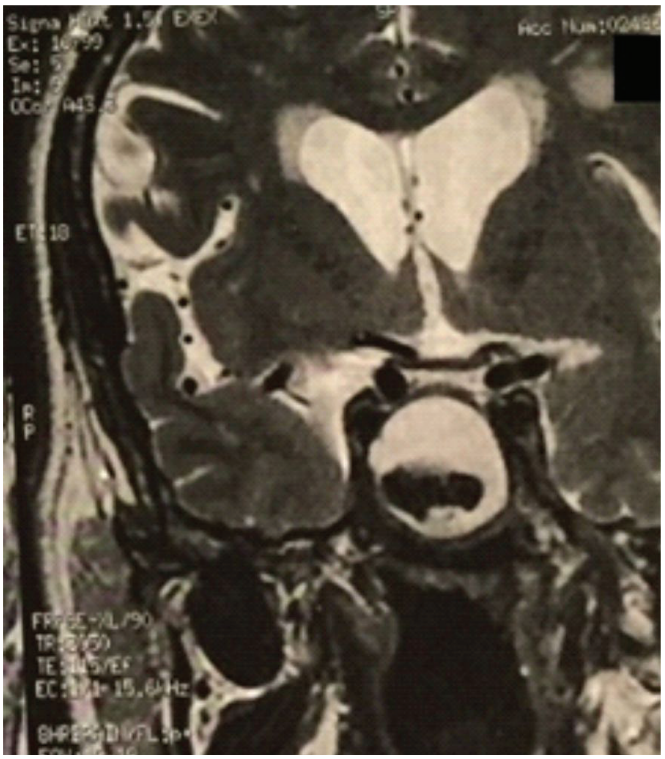

Figure 3. Heterogeneous expansive lesion at sellar region

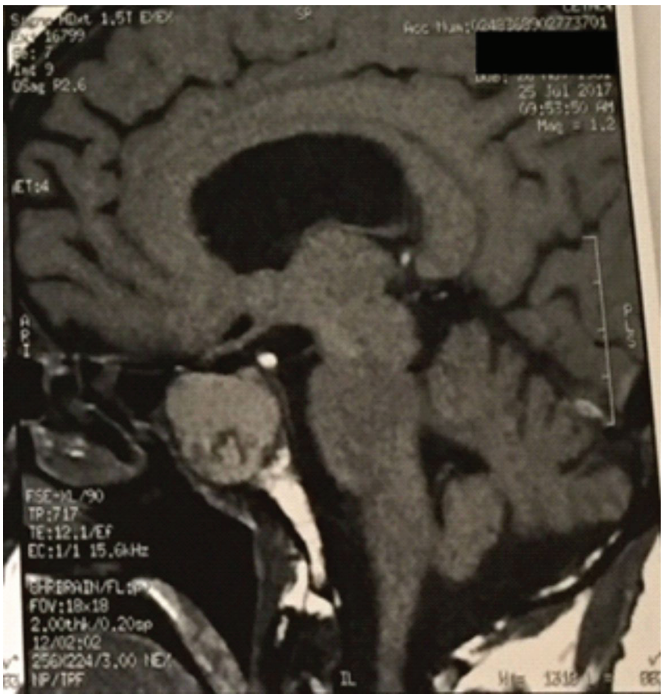

Figure 2. Heterogeneous expansive lesion at sellar region n

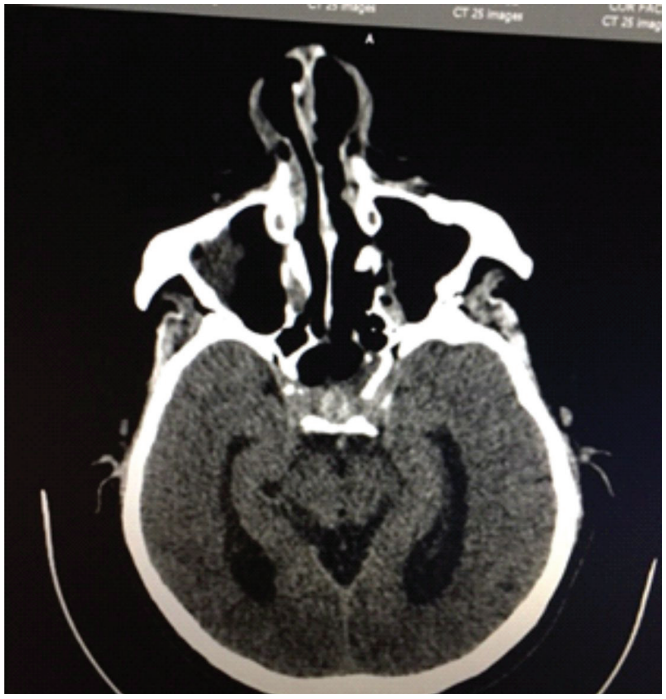

Figure 4. Material at maxillary sinus on the right with liquid level

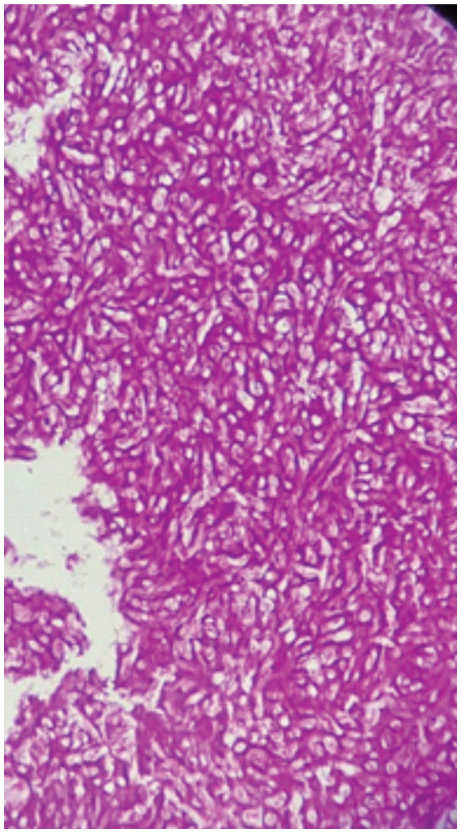

Figure 4. Hyalohyphomycosis on pituitary chirurgical piece

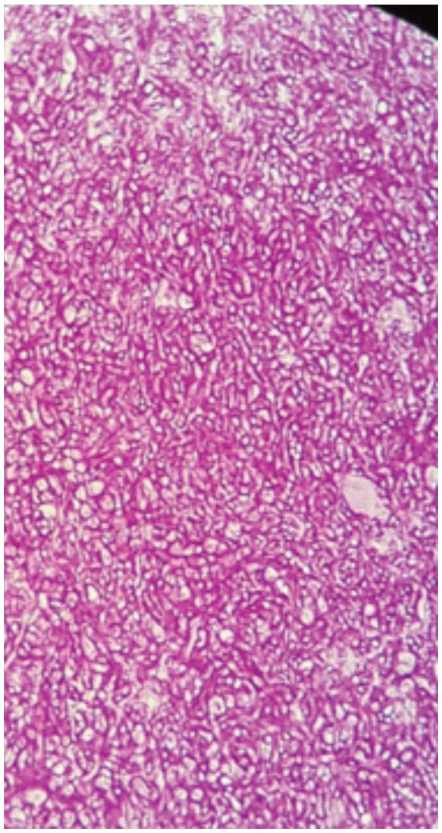

Figure 5. Hyalohyphomycosis on pituitary chirurgical piece

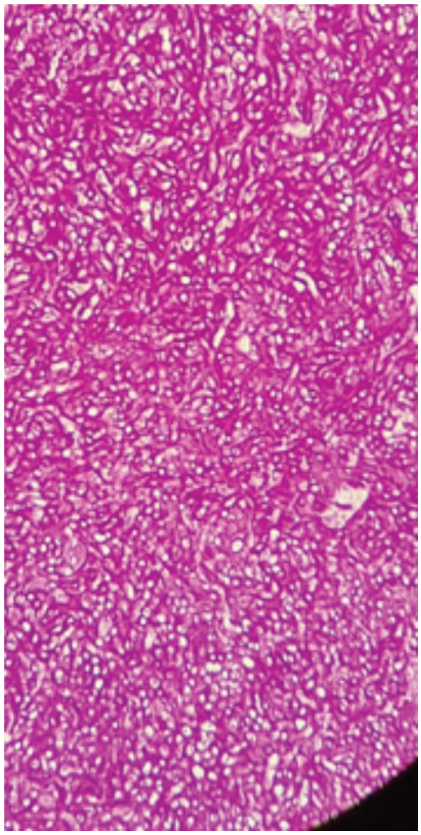

Figure 6. Hyalohyphomycosis on pituitary chirurgical piece

DISCUSSION

Mucormycosis is a life-threating infection caused by fungi of the order *Mucorales*. Recent reclassification has abolished the order Zygomycetes and placed the order *Mucorales* in the subphylum *Mucormycotina* (3). This rare and highly invasive infection occurs preferentially in immunosuppressed individuals (4). Rhino-orbital-cerebral and pulmonary infections are the most common syndromes caused by these fungi (1). The most common etiological agent is *Rhizopus oryzae*, that is responsible for 60% of all forms of mucormycosis, along with *Mucor* and Absidia (5). *Cunninghamella, Absidia, Saksenaea*, and *Apophysomyces* are genera that are less commonly implicated in infection (1).

Rhizopus organisms have an enzyme, ketone reductase, which allows them to thrive in high glucose, acidic conditions. Serum from healthy individuals inhibits growth of *Rhizopus*, whereas serum from individuals in diabetic ketoacidosis stimulates growth. Rhino-orbital-cerebral and pulmonary mucormycosis are acquired by the inhalation of spores. In healthy individuals, cilia transport these spores to the pharynx and they are cleared through the gastrointestinal tract. In susceptible individuals, infection usually begins in the nasal turbinates or the alveoli. The agents of mucormycosis are angioinvasive; thus, infarction of infected tissues is a hallmark of invasive disease (1).

Mucormycosis typically occurs in patients with diabetic ketoacidosis or poorly controlled diabetes, patients receiving chemotherapy by lymphoproliferative disease or another neoplasia, or under corticoid therapy, patients that have received organ or hematopoietic stem cell transplant and even in patients without apparent predisposed factors (6). Other underlying risk factors include AIDS, trauma, treatment with deferoxamine, use of intravenous drugs and malnutrition (1). The number of cases is increasing constantly, mostly dependent on the prevalence of the risk factors cited above as well as by the increased lifespan of those on immunosuppress therapy and general population (6). A review of 929 cases of mucormycosis that were reported between 1940 and 2003 noted that diabetes mellitus was the most common risk factor, found in 36% of cases, followed by hematologic malignancies (17%) and solid organ or hematopoietic cell transplantation (12%). In some patients, mucormycosis was the diabetes-defining illness. In a later study of 101 patients diagnosed with mucormycosis between 2005 and 2007 in France, hematologic malignancy was the most common risk factor, occurring in 50% of patients, followed by diabetes in 23% and trauma in 18% of cases (1).

The number of reported cases of mucormycosis in diabetic patients in the United States has declined since the 1990s, a trend that has not been noted in France or in developing countries. One hypothesis that has been suggested to explain the decline in the United States is the widespread use of statins, which have inhibitory activity in vitro against a wide range of the agents of mucormycosis (1).

The incidence of this infection in Brazil is unknown, there are only a few case studies that were published, however there is a trend for predominance of cases on the North and North West regions of Brazil (7).

The infection usually presents as acute sinusitis with fever, nasal congestion, purulent nasal discharge, headache, and sinus pain. All of the sinuses become involved, and spread to contiguous structures, such as the palate, orbit, and brain, usually progresses rapidly. However, this disease can be also manifested in conjunction with fever, lethargy, headaches, retro-orbital pain, abrupt vision loss, proptosis, periorbital cellulitis, epistaxis and convulsions (1,7).

The trademarks of spread beyond the sinuses are tissue necrosis of the palate resulting in palatal eschars, destruction of the turbinates, perinasal swelling, and erythema and cyanosis of the facial skin overlying the involved sinuses and/or orbit (3). Spread from the sphenoid sinuses to the adjacent cavernous

sinus can result in cranial nerve palsies, thrombosis of the sinus, and involvement of the carotid artery. Hematogenous spread to other organs is rare unless the patient has an underlying hematologic malignancy with neutropenia (1).

Central nervous system (CNS) mucormycosis usually arises from an adjacent paranasal sinus infection. Yet, there have been more than 30 cases of isolated CNS mucormycosis described in the literature. Infection is thought to result from seeding of the brain during an episode of fungemia, analogous to renal involvement. Over two-thirds of the patients with isolated CNS mucormycosis have been intravenous drug users who presumably have injected material contaminated with fungi directly into the bloodstream. Some of the patients with isolated CNS mucormycosis have had HIV infection in addition to drug use (1).

The fact that mucormycosis is a rare human infection reflects the ineffectiveness of early diagnosis of this disease. The first suspect evoking sign for rhino-orbital-cerebral infection is periorbital edema with orbital pain or the presence of erythema and painful palate edema. Its progression to cutaneous or mucus necrosis happens within hours, which can be preceded or not by mucopurulent or bloody rhinorrhea. Subsequently there is the association of fever of variable intensity, migraines, signs of toxemia and alterations of general health status. This might be the best timing for presumptive diagnostic that can result on better prognostic (6).

Clinical diagnosis of patients with suspected rhino-cerebral mucormycosis should consider the following: orbital cellulitis, thrombosis of cavernous sinus, fast growing orbit tumor, aspergillosis, infection by *Ilescheria boydii* (the asexual form: *Scedosporium apiospermum*) (*psedallescheriasis*) and *Pseudad Fusarium infection*. Aspergillosis, pseudallescheriasis, fusariosis, nocardiosis, Wegner's granulomatosis, pulmonary emboly and malignancy also should be considered when diagnosing a patient with suspected pulmonary mucormycosis. Regarding cutaneous disease, ecthyma gangrenosum associated to pseudomonas and anthrax infections should be considered. Considerations about gastrointestinal disease should include intestinal obstruction and ilocecal tuberculosis (2).

Clinical suspicious of mucormycosis is an indicative for initiating treatment. Patients with suspected rhinocerebral disease should undergo emergent computed tomography (CT) imaging of the paranasal sinuses and an endoscopic examination of their nasal passages with biopsies of any suggestive lesions. The diagnosis of mucormycosis is stablished by obtaining a biopsy specimen of the involved tissue, and frozen tissue samples should be immediately evaluated for signs of infection. Tissue should also be sent for routine pathology examination and cultures. Swabs of tissue or discharge are unreliable (2). For pulmonary disease, a bronchoalveolar lavage (BAL), biopsy, or both may assist in the diagnosis. For cutaneous disease, a skin biopsy for pathology and culture should be obtained (2).

A complete blood cell count (CBC) should be obtained to assess for neutropenia. A chemistry panel that includes blood glucose, bicarbonate, and electrolytes is useful to monitor homeostasis and direct correction of acidosis. Iron studies may be indicated to assess the presence of iron overload as shown by high ferritin levels and a low total iron-binding capacity (2). In cases of central nervous system (CNS) involvement, cerebrospinal fluid (CSF) findings may include elevated protein levels and a modest mononuclear pleocytosis. CSF cultures are typically sterile. A CT scan should precede a lumbar puncture to assess for evidence of elevated intracranial pressure, which could lead to herniation (2).

Blood cultures can be obtained; however, they are usually negative despite the angioinvasive nature of the organism. Blood cultures may be useful to detect bacteremia as an independent predictor of 28-day mortality. There are no specific biomarkers to identify mucormycosis. Bronchoalveolar lavage (BAL) of fluid culture has a low yield, with sensitivity of 20-50%. Antigen tests (beta-D-glucan or galactomannan) are not useful for detecting this infection (2).

The use of quantitative polymerase chain reaction (qPCR) for detection of circulating DNA from common Mucorales species (*Lichtheimia species, Rhizomucor species*, and *Mucor/Rhizopus species*) while not yet commercially available, has been described and appears promising for the early diagnosis of mucormycosis in high-risk patients. In a retrospective analysis of 44 cases, qPCR identification was fully concordant with that of culture. Assay positivity was observed at an average of 9 days, at least 2 days prior to positive imaging findings. Development of PCR negativity after treatment was associated with higher survival rates (48% vs 4%), suggesting that this modality could eventually be used for treatment monitoring (2).

Imaging should be used to investigate areas of suspected mucormycosis. Because of subclinical disease may be present, a detailed history and physical examination are recommended in addition to imaging (CT) of the brain, sinuses, chest, and abdomen (2).

In relation to rhinocerebral infections, plain films may show sinus involvement with mucosal thickening, air-fluid levels, and/or bony erosions (2). Head and facial CT imaging should be used as the initial investigation in rhinocerebral infections. CT scans may show sinusitis of the ethmoid and sphenoid sinuses, as well as orbital and intracranial extension. As the disease progresses, bony erosion may occur and the infection may spread into the brain or orbits. Furthermore, because mucormycosis organisms have a predilection for vascular involvement, thromboses of the cavernous sinus or internal carotid artery may occur. All of the areas of involvement must be understood in order to plan the extent of surgical debridement. Magnetic resonance imaging (MRI) of the facial sinuses and brain is superior to a CT scan in assessing the degree of tissue invasion and need for ongoing surgery (2).

CT scanning or MRI of the central nervous system may reveal abscesses (specially in the setting of intravenous drug use) or extension of rhinocerebral disease into the brain. Cavernous and, less commonly, sagittal sinus thrombosis may also be seen (2).

TREATMENT

Treatment of mucormycosis involves a combination of surgical debridement of involved tissues and antifungal therapy. Exclusion of predisposing factors for infection, such as hyperglycemia, metabolic acidosis, deferoxamine administration, and neutropenia, is also fundamental (1).

The drug of choice for initial therapy of mucormycosis is a lipid formulation of amphotericin B. Posaconazol or isavuconazole can be used for oral step-down therapy for patients who have responded to a lipid formulation of amphotericin B. Posaconazol or isavuconazole can be also used as salvage therapy for patients who do not respond to or cannot tolerate amphotericin B; for salvage therapy, the decision to use intravenous or oral posaconazole or isavuconazole depends on how ill the patient is, whether an initial course of amphotericin B was able to be administered, and whether the patient has a functioning gastrointestinal (GI) tract. Aggressive surgical debridement of involved tissues should be undertaken as soon as the diagnosis of any form of mucormycosis is suspected. In the case of rhinocerebral infection, debridement to remove all necrotic tissue will often be disfiguring, requiring removal of the palate, nasal cartilage, and the orbit (1).

In one study, amphotericin B lipid complex resulted in a 71% success rate as salvage therapy for mucormycosis. Furthermore, treatment with liposomal amphotericin B (LAmB) was associated with 67% survival rate (16 of 24 patients) compared

with 39% survival (24 of 62 patients) with amphotericin B deoxycholate (P = 0.2) among patients with cancer who experienced mucormycosis (3).

The usual starting dose is 5 mg/kg daily of liposomal amphotericin B or amphotericin B lipid complex, and many clinicians will increase the dose up as high as 10 mg/kg daily in an attempt to control this infection (1). The optimum dosages for treatment of mucormycosis are not known for any antifungal agent (3).

Overall mortality from rhino-orbital-cerebral mucormycosis ranges from 25 to 62 percent, with the best prognosis in patients with infection confined to the sinuses. The prognosis is especially poor for patients with brain, cavernous sinus, or carotid involvement, although some patients with these complications have been cured of the infection. The outcome in patients with pulmonary mucormycosis is worse than for patients with rhino-orbital-cerebral involvement, with mortality rates as high as 87% (1).

CONCLUSION

Being a delayed treatment an independent factor for poor outcome, a successful result is base on a high level of clinical suspect of the disease and its associated risk factors, thus making it possible to obtain early diagnosis and appropriate combine surgical-medical management.

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Correspondence to: Guilherme Gabardo Adriano
R. Irmã Flávia Borlet, 990 – Hauer, Curitiba-PR.

CASE REPORT
HYPEROSMOLAR HYPERGLYCEMIC STATE: CASE REPORT
ESTADO HIPERGLICÊMICO HIPEROSMOLAR: RELATO DE CASO

FERNANDA DA SILVA MILIORINI[1]
JAQUELINE FORESTIERE BOLONHEZ[1]
ESTELLA THAISA SONTAG DOS REIS[1]
HUGO LEONARDO SHIGENAGA RIBEIRO[2]
SIDNEY SENHORINI JUNIOR[3]

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Descritores: Estado hiperglicêmico hiperosmolar; Crise aguda hiperglicêmica; Diabetes mellitus

Resumo

Em linhas gerais o estado hiperglicêmico hiperosmolar (EHH) pode ser definido como uma complicação aguda característica de pacientes, em sua maioria, portadores de DM que evoluem com hiperglicemia, aumento da osmolaridade e desidratação. Manifesta-se com sinais e sintomas de descompensação típicos do diabetes. O diagnóstico é baseado em critérios clínicos e laboratoriais que deve ser identificado precocemente para evitar sua progressão e agravamento. Desta forma, o presente estudo tem por objetivo relatar um caso de EHH diagnosticado e tratado adequadamente que evoluiu de forma satisfatória e verificar, com base na literatura, os critérios diagnósticos e terapêutica indicada no manejo desses pacientes. **Endocrinol diabetes clin exp 2018 2033 -2035.**

Abstract

In general terms the hyperosmolar hyperglycemic state (HHS) can be defined as an acute complication characteristic of most diabetics patients that evolves with hyperglycemia, hyperosmolarity and dehydration. It manifests with signs and symptoms of decompensation of diabetes. The diagnosis is based on clinical and laboratory criteria that must be identified early to avoid the progression and aggravation. Thus, this study aims to report a case of HHS diagnosed and treated properly which has progressed satisfactorily and, based on the literature, verify the diagnosis criteria and therapy indicated in the management of these patients. **Endocrinol diabetes clin exp 2018 2033 -2035.**

INTRODUCTION

The Hyperglycemic Hyperosmolar State (HHS) is the main form of metabolic decompensation in Type II Diabetes Mellitus, according to the following criteria: glycemia ≥600 mg/dL, serum osmolarity >320 mOsm/kg and serum bicarbonate >15 mEq/L with discrete ketonemia or absent. The clinical picture evolves in days to weeks with typical symptoms of decompensated diabetes such as polyuria, weight loss, polydipsia, drowsiness, torpor and coma in more severe cases. The treatment consists of vigorous volemia replacement, electrolytic replacement, insulin administration, precipitating factors and prevention in intensive care unit if cardiovascular instability. 1.2 This study aims to report a case of late diagnosis of HHS in a patient admitted initially with mental confusion who was not valued for having frontotemporal dementia and a review based on the literature on pathophysiology, diagnostic criteria and treatment of this pathology.

CLINICAL CASE

J.S., 60 years old, married, retired, was admitted to the Emergency Care Unit located in the South Zone in Maringá, after checking blood glucose >600 mg/dL in his Basic Health Unit. Companion refers to urinary incontinence, urinary urgency and confusion for one week. He evolved with worsening of the general state, mental confusion and drowsiness. The companion denied Diabetes Mellitus and Hypertension. He reported frontotemporal dementia using Memantine 15mg/day and Quetiapine 50mg/day. At admission he was prostrated, drowsy, confused, dyspneic and with signs of severe dehydration. Vital signs were hypotensive, 94% of saturation with 2L/min nasal catheter, normothermic, with capillary glycemia >600 mg/dL. Started serum therapy with SF 0.45% 1000ml EV 12/12h and Regular Insulin 100UI + SF 100ml in BIC 7ml/h. Subsequently, the patient was referred to the Memorial Hospital of Maringá, where tests were performed that demonstrated plasma osmolarity of 408 mOsm/kg, blood glucose of 581 mg/dL, HCO3 = 19.6 mmol/L, corrected hypernatremia of 177 mmol/L, hypermagnesemia with value of 3.9 mg/dL and Urea of 134 mg/dL, being taken to the hospital ICU. It was performed vigorous volemia replacement, correction of electrolytes disturbances and basic acid, reduction of hyperglycemia and osmolarity. He was discharged after 11 days of evolution with clinical improvement.

DISCUSSION

The hyperosmolar hyperglycemic state (HHS) is a syndrome that consists of high levels of glycemia, hyperosmolality and dehydration, but without the presence of ketoacidosis. It occurs due to insulin deficiency with increased levels of hormones against regulators such as glucagon, cortisol, growth hormone and catecholamines (1,2).

The first report of HHS was described in 1880 by von Frerichs and Dreshfeld with patients with an uncommon type of diabetes presenting with coma, glycosuria and hyperglycemia in the absence of ketonuria, kussmaul breathing and ketone breath (3).

The incidence and prevalence are high in elderly individuals with type 2 diabetes mellitus (T2DM) since diabetes is a chronic disease with high rates of emergency care. In Finland is found the highest incidence rate of HHS (4).

The average age is found between 54.6 ± 9.4 years with mean glycemia of 956 ± 267 mg/dL, Hb A1c of 12.5 ± 2.75% and osmolality of 349.4 ± 34.3 mOsm/L. The mortality rate stands at 20% (5).

It is considered a rare presentation when it is associated with type 1 diabetes mellitus (T1DM), especially in children because it has high morbidity and mortality (6,7,8).

However, there is a report in the literature of cases of HHS in non-obese children and adolescents with T1DM, despite being more associated with T2DM and obesity as a risk factor (9).

Mortality in HHS presents in 20% being greater when compared to DKA representing 15% of the cases compared to a 3,4-4,6% of cases in DKA. Therefore, the mortality in HHS is three times higher compared to DKA. The prognosis

[1]Academic of the graduation course in Medicine of the Faculty Ingá;
[2]Clinical Medicine at the Memorial Hospital of Maringá
[3]Postgraduate courses at NECPAR, PUC-PR, UNINGÁ , Maringá, Paraná, Brazil.
E-mail: fermiliorini@hotmail.com

is worse when it affects elderly individuals over 65 years or in the presence of hypotension or coma. The main cause of HHS are infections such as pneumonia in 40-60% of the patients, besides the urinary tract infection (5-16%). In 20% of the cases there is no diagnosis of associated DM. It may be associated with stroke, myocardial infarction and trauma (5,10,11,12,13).

In addition, it is believed that some medications may be involved in the development of HHS such as thiazides, glucocorticoids, phenytoin, beta-blockers and atypical antipsychotics (12,13)

Serious complications may be associated as cerebral edema, rhabdomyolysis, acute renal failure, and malignant hyperthermia (14,15).

Increased glycemia is caused by increased gluconeogenesis and glycogenolysis associated with peripheral glucose conversion. When extracellular levels of glucose increase, osmolality increases and there is water flow from the intracellular to the extracellular due to the osmolarity gradient. Thus, the rate of glomerular filtration increases and, consequently, glycosuria and osmotic diuresis rise to avoid an increase in glycemia. However, although glycosuria initially prevent the increase in glycemia, with increased osmotic diuresis generates hypovolemia. Thus, the glomerular filtration rate reduces and glucose returns to high levels. Studies indicate that high levels of insulin and glucagon prevent the development of ketoacidosis, a characteristic that distinguishes HHS from individuals who develop DKA (16). In addition, hyperglycemia is associated with the release of high levels of proinflammatory cytokines such as interleukins 6 and 8, tumor necrosis factor (TNF alpha) and reactive oxygen species (17).

The increase of reactive oxygen species generates lipid peroxidation, protein carbonylation and DNA damage, as well as reduction of cerebral perfusion by the reduction of nitric oxide(18). The lack of sodium derived from its intracellular outlet is believed to cause a hypertonic state that when not compensated by brain cells increases the risk of migration of inflammatory factors to the central nervous system (19).

Acute hyperglycemic crises may manifest clinically with similar characteristics in EHH and CAD. The diagnosis of HD is based on some criteria reported by Gerich et al and Arieff and Carroll's in 1971 that established a glucose level above 600mg/dL, total serum osmolarity above 350 and a serum acetone reaction of 0 to 2 (20,21).

According to the American Diabetes Association (ADA) and international guidelines the diagnosis is established when glucose is above 600mg/dL, osmolarity above 320mOsm/L in the absence of ketoacidosis (22,23). Although clinical manifestations of HHS are similar to DKA, in HHS, glycemia, dehydration and serum sodium tend to be higher and associated with absent or mild ketonemia. Thus, the clinical manifestations of DKA and HHS present slowly and progressively with signs and symptoms of decompensated DM. Nausea (83%), vomiting (78%), polyuria (75%), polydipsia (74%), weight loss (43%), polyphagia (33%), besides drowsiness, torpor and coma may be present. Dehydration can still cause dry and cold skin, dry tongue, eyeball hypotonia, cold extremities, agitation, hyperemic facies, muscle hypotonia, rapid pulse and blood pressure (24).

In addition, the dehydration picture may simulate acute abdomen, as it interferes with the sliding of the pleura and peritoneum leaflets, which may cause atony and gastric stasis, aggravating the picture of vomiting (25,26).

For the laboratorial diagnosis it is included a blood count for the identification of infectious and hematocrit processes, plasma glucose, electrolytes, urea, creatinine, ketonemia, anion gap calculation, urine test to identify ketonuria, and arterial blood gas analysis to evaluate leukocytosis acid balance, and electrocardiogram (5).

The glycemia will always be increased, reaching values above 1000 mg/dl.

Regarding Glycosuria and Ketonuria in HHS, ketonuria is negative or weakly positive (+). The electrolytes (Na+, K+, Cl-, PO4 (, Ca++, Mg++) will be low. Urea and Creatinine may be elevated in ketoacidosis due to protein catabolism and dehydration, but if too high may indicate prior or recent renal failure. Among the criteria for laboratory and clinical control are osmolality <315 mOsm/kg and alert patient (27).

Treatment includes vigorous volemic replacement, electrolyte replacement, insulin administration, diagnosis of precipitating factors and prevention. It should be done in intensive care unit if cardiovascular instability (28,29).

It aims to correct endocrine disorders, hydroelectrolytic and acid-base disorders. It is recommended hydration for the reduction of hyperglycemia, against the regulatory factors and improvement of renal perfusion with isotonic saline (0.9%) 15-20mL/kg in the first to second hour followed by 250-500mL/h until resolution of the crisis, in addition to potassium replacement with 4-5mEq/L if levels below 5.5mEq/L (30).

It is important to monitor plasma sodium levels to prevent cerebral edema and cerebral pontine myelinolysis and correct blood osmolarity if necessary. After hydration therapy, insulin at a dose of 0.05UI/kg/h should be administered for glucose reduction in order to avoid hypokalemia and excessive reduction of serum osmolarity(14).

During hydration, the level of electrolytes and diuresis are monitored. If the electrolytes are normal or elevated, hypotonic saline solution of 0.45% NaCl 4 to 14 ml/kg/ hour or 250 to 500 mL/h can be administered. If the levels are low continue with Isotonic NaCl solution 0.9% 1.16(27).

In a cohort performed with patients with T2DM and HHS for one year, there was an increase in the risk of developing stroke in 9.5% compared to 5.2% in patients with T2DM in the absence of HHS (31).

However, the use of anticoagulant is still uncertain in patients with hyperglycemia. Some studies point to the increased risk of thrombotic events that is lower when compared to cases of ketoacidosis. Before initiating insulin therapy, potassium should be dosed to verify if it is above 3 mEq/L (32,33).

Insulin has the function of reducing glucose, antioxidant and anti-inflammatory action (27).

The administration of 5UI of single intramuscular insulin every 2 hours or every 4 hours is indicated until the patient returns to feed and the fixed dietary insulin regimen can be done. Culture collection is recommended in patients who have manifested hypotension and initiation of antibiotic therapy if necessary, in addition to the evaluation of the medications administered by the patient that may have precipitated the crisis by removing them if necessary (34,35,36,37).

Treatment of cerebral edema includes 1-2 g/kg of mannitol in 30 minutes and intravenous dexamethasone (Decadron) and its prevention with slow volemic replacement. The symptoms of encephalopathy may be present when levels above 160 mEq/L of serum sodium and total osmolality of 340 mOsm/kg and effective 320 mOsm/kg. Therefore, it is recommended to maintain glucose levels around 300 mg/dL in order to prevent cerebral edema (38,39,40).

Among the complications associated with the treatment are myocardial infarction, mesenteric artery occlusion, disseminated intravascular coagulation and low flow syndrome (41,42,43).

As hyperglycemia and glycosuria generates loss of water and electrolytes through the urine and leads to a state of hyperosmolarity. Osmolarity is an indicator of severity and can be used to follow up treatment (44,45,46).

CONCLUSION

Based on the literature it is possible to verify that HHS is a serious acute complication of a comorbidity with high incidence such as DM, in which the identification of the susceptible patients according to the clinical situation in which diagnosis and

treatment of precocious form can prevent unfavorable outcomes and reduce the morbidity and mortality of this pathology. However, additional studies regarding therapy are indispensable, and it is essential to identify the risk factors and prevent their development.

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Correspondance: Fernanda Miliorini
Rua São Paulo 881, Centro. Eldorado-MS CEP: 79970-000.

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