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DIAGNOSIS OF ADRENAL INSUFFICIENCY INDUCED BY GLUCOCORTICOIDS

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Abstract: Adrenal Insufficiency (AI) corresponds to the inability of the adrenal gland to produce adequate amounts of adrenocortical hormones and can be caused by prolonged use of glucocorticoids. In these cases, despite the rarity of this etiology, the presentation of patients with shock or hypotension, together with non-specific and potentially fatal symptoms, characterizes a clinical emergency. Due to the severity of this problem, the objective of the study was to review the literature regarding adrenal insufficiency, in order to choose the best diagnostic approach for patients using glucocorticoids. The methodology was an integrative review of the literature, searching for the descriptors "adrenal insufficiency", "diagnosis" and "glucocorticoids" in the MEDLINE and LILACS databases, selecting filters for English and Portuguese. From publications carried out between 2018 and 2023, five works were chosen for study. As a result of the research, it was observed that diagnostic procedures for adrenal insufficiency induced by glucocorticoids imply the correct collection of the clinical history, focusing on the symptoms and medications used or that were suspended without guidance Furthermore, this etiology demonstrated the greatest number of symptoms, such as fatigue, skin hyperpigmentation and weight loss. Body mass index and waist circumference were higher when compared to primary adrenal insufficiency, however the best clinical indicators of adequate replacement of glucocorticoids were the symptoms reported by the patient, such as appetite and well-being. In children, the approach is similar, accompanied by periodic dose adjustment. And, regarding complementary exams, the rapid stimulation test with ACTH, followed by serum cortisol measurement is the gold standard, other dosages help to differentiate the etiologies. Finally, careful collection of clinical history, physical examination and complementary tests are vital to confirm the diagnosis of adrenal insufficiency and avoid negative outcomes.

Keywords: Adrenal insufficiency. Glucocorticoids. Diagnosis.

INTRODUCTION

Adrenal Insufficiency (AI) corresponds to the inability of the adrenal gland to produce adequate amounts of adrenocortical hormones. This problem may be caused by prolonged use of glucocorticoids, as there is suppression of the corticotroph axis. Therefore, although this etiology is uncommon, its diagnosis must be assertive, due to the presentation of patients with shock or hypotension, together with non-specific and potentially fatal symptoms, characterizing a clinical emergency.

GOAL

Review the literature on adrenal insufficiency in order to choose the best diagnostic approach for patients using glucocorticoids.

METHODOLOGY

This is an integrative review of the literature, produced from primary and secondary sources, with a search in the MEDLINE and LILACS databases. To this end, the following descriptors were added to the search fields and "Research details": "adrenal insufficiency", "diagnosis" and "glucocorticoids". Filters were then selected for sampling articles in English and Portuguese, published between the years 2018 and 2023, reaching a total of 156 articles. Of the total, 136 articles were excluded after analyzing the title, with the summary of the remaining 20 being read. Finally, 5 studies were chosen to prepare the present work.

RESULTS AND DISCUSSION

The final sampling of the review was established by five scientific articles, selected according to the previously established inclusion criteria. Table 1 presents the main information from each of the articles and makes it possible to observe the still scarce availability of studies on the diagnosis of adrenal insufficiency, despite its importance and potential severity.

The report produced by AFIAT, T.-P. et al., for example, corroborates the idea that the later the diagnosis of adrenal insufficiency is, the worse the prognosis. In this case, the 53-year-old patient, who underwent transarterial hepatic embolization due to metastasis, suffered an adrenal crisis that led to his death. This is because, according to the author himself, there were no electrolyte changes and the hypoglycemia was attributed to the well-known non-islet cell tumor hypoglycemia (NICTH). The author also recognized that hormonal imbalance is more expected than electrolyte changes, which delayed the recognition and treatment of IA.

From this, we can see the importance of knowing the most effective approach in relation to the diagnosis of AI. This feat was made possible by tracing a characteristic epidemiological profile, as done by S. Puglisi and A. Rossini et al. and also Li D, Genere N. and Behnken E, et al., in their respective studies.

For S. Puglisi and A. Rossini et al., the impact of the use of glucocorticoids on adrenal insufficiency is an aspect that has been little evaluated. Given this fact, the retrospective study of medical records aimed to predict the influence of sex and body weight on the dosage of glucocorticoids in different etiologies of AI. The researchers demonstrated that in secondary AI the dose was based on weight and that overdose was more common in primary AI.

However, more relevant to this review were the data collected in the two consultations carried out at different times. Thus, at first, differences in clinical characteristics and comorbidities were not evident; In the second consultation, however, a higher blood pressure level and BMI were found in secondary AI and a higher frequency of adrenal crises in cases of primary AI.

In the work of Li D, Genere N, Behnken E, et al., 696 patients were included as study participants, being categorized according to the etiology of AI, into three groups: PAI (primary adrenal insufficiency), SAI (secondary adrenal insufficiency) and GAI (glucocorticoid-induced adrenal insufficiency). Next, several data were collected in order to evaluate "self-reported" disease and relate it to clinical components of the different AI subtypes.

Among the parameters used, the most important are sex, age at diagnosis, ethnicity, number of symptoms and lack of knowledge about the diagnosis itself. This way, a profile was drawn with a predominance of women, with a median age at diagnosis equivalent to 58 years and of Caucasian ethnicity. The frequency of cases was distributed between 291, 226 and 179 for the PAI, SAI and GIAI subtypes, respectively. Regarding the number of symptoms at the time of diagnosis, those with GIAI ranked second in terms of lack of knowledge about the diagnosis, but had the highest number of symptoms – with a median of four symptoms, ranging from fatigue, darkening of the skin, weight loss, decreased appetite, craving for salt, fainting, low blood pressure, low blood sugar levels, muscle weakness and cramps, mental confusion, joint pain, diarrhea and others. This same group also reported symptoms suggestive of excessive glucocorticoid replacement, such as hypertension, hyperglycemia, irritability, edema or weight gain.

Furthermore, the research identified

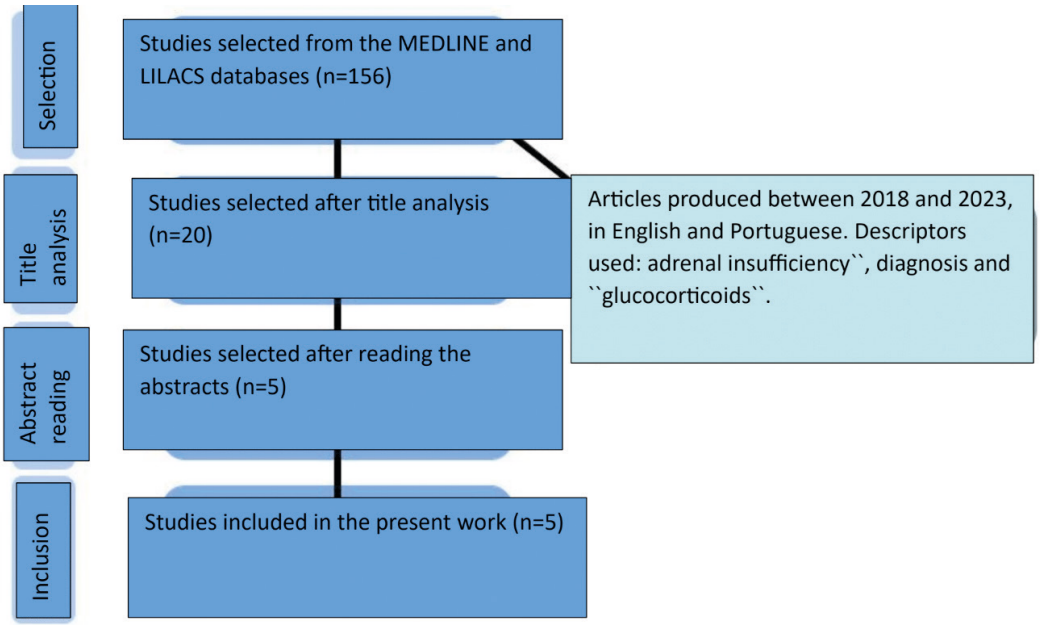

Table 1: selection of literature

Author/ year	Article title	Type of production	Main results
AFIAT, T.-P. et al. (2021)	Adrenal crisis and death following transarterial chemoembolization of sarcoma liver metastases	Case study	Electrolyte changes occur less frequently than hormonal imbalance during an adrenal crisis, and late identification and initiation of treatment are common causes of unnecessary deaths due to a preventable and treatable problem.
S. Puglisi e A. Rossini et al. (2020)	What factors have impact on glucocorticoid replacement in adrenal insufficiency: a real-life study	Retrospective observational study	At the first consultation, the clinical picture of primary and secondary AI is similar, however, at the last consultation, characteristics such as weight, BMI, waist length and blood pressure levels are higher in secondary AI.
Li D, Genere N, Behnken E, et al. (2021)	Determinants of Self-reported Health Outcomes in Adrenal Insufficiency: A Multisite Survey Study	Cross-sectional study	Of patients with glucocorticoid-induced AI, 37% had at least one adrenal crisis event since diagnosis. However, these cases could be prevented by greater understanding of the diagnosis and adherence to treatment by patients, in addition to greater training of professionals in recognizing referred symptoms, since they appear in greater numbers in this group.
HIMES, C. P. et al. (2020)	Perioperative Evaluation and Management of Endocrine Disorders	Guideline	In patients who are chronic users of corticosteroids, the need for a supplementary dose must be analyzed, which is determined according to the invasiveness of the operation, the dose and duration of exposure to corticosteroids and by additional tests of the corticotrophic axis. This precaution makes it possible to identify these problems before surgery, to avoid complications.
KANTHAGNANY, S.-K. et al. (2021)	Fifteen-minute consultation: An approach to the child receiving glucocorticoids	Diagnostic study	Children with AI may not have obvious clinical characteristics, but signs of altered fat distribution, central adiposity, hirsutism, easy bruising and muscle loss must be minimally investigated. Blood pressure levels and glycosuria are also important data.

Table 1: Studies included in the analysis of the integrative literature review

IA: Adrenal insufficiency

that 37% of patients with GAI have had at least one episode of adrenal crisis since diagnosis, with a lower recurrence only in relation to individuals with AIP. Patients with glucocorticoid-induced adrenal insufficiency also had the highest proportion of negative experiences with emergency departments.

Li D, Genere N, Behnken E, et al., therefore, conclude that the delay in diagnosis and the little education offered to patients about this problem are gaps, making it possible to overcome the situation by testing for AI and making time available to inform patients and family members about the disease.

HIMES, C. P. et al., in 2020, in the preoperative context, reiterated that cortisol secretion rarely exceeds 200 mg/d after surgery and is generally at a third of that value in less invasive procedures. Still, there are many unanswered questions about who needs a supplemental dose of corticosteroids. The article recommends supplementation without additional testing for patients with primary AI or secondary to hypopituitarism, for those with Cushing's syndrome secondary to the use of corticosteroids, for users of doses greater than or equal to 5 mg of prednisone daily for more than three weeks and in the last three months and for those receiving high doses of inhaled corticosteroids.

Additional tests must be carried out in categories that were not mentioned, such as people exposed to corticosteroids (5mg of prednisone per month at least three weeks), with tests that evaluate the corticotrophic axis – measurement of cortisol (serum or plasma) and baseline plasma ACTH, as well as rapid ACTH stimulation test. Therefore, patients receiving long-term corticosteroid therapy require supplementary doses, determined by the invasiveness of the operation, the dose and duration of corticosteroid to which they are exposed and examinations of the hypothalamic-pituitary-adrenal axis.

Looking back at the diagnosis of IA in children, KANTHAGNANY, S.-K. et al., choose as main symptoms dizziness, nausea, fatigue, anorexia, muscle weakness and pain, changes in mood, weight loss and poor growth. Adrenal crises are accompanied by worsening weakness, vomiting, confusion, hypoglycemia, hypotension and even convulsions.

This work recommends reviewing the doses for any child using glucocorticoids for more than seven days, with it being important to adjust the dosage according to the expected therapeutic effect, the presence of the aforementioned symptoms and the regimen of use adopted.

Upon examination, it is known that many children do not present an evident clinical picture, but research must be carried out on altered fat distribution, central adiposity, hirsutism, easy formation of bruises and muscle loss. Blood pressure measurement and urinalysis to check glycosuria are also valid measures, along with serial measurement of height and weight, indicating poor growth.

The investigation must also include testing for morning cortisol and ACTH, a common recommendation for most children using glucocorticoids. Furthermore, during an adrenal crisis, some of the most serious symptoms present themselves and the approach must be carried out as for any other child, using the ABCDE, followed by key characteristics that support the diagnosis, such as hypoglycemia, hyponatremia and refractory hypotension.

The literature then culminates in diagnostic measures that must take into consideration, the clinical picture, reported symptoms and cortisol and ACTH levels, as ways to avoid the worst outcomes.

FINAL CONSIDERATIONS

In short, given the urgency that cases of adrenal insufficiency can represent, especially those resulting from prolonged use of glucocorticoids, it is of great importance to meticulously observe the patient's clinical history, as it provides valuable information regarding the previous use of glucocorticoids. glucocorticoid medications and possible abrupt suspension by patients. Furthermore, physical and complementary examinations (such as the ACTH stimulation test) are vital to confirm the diagnosis, due to the non-specific symptoms and the variety of etiologies of this pathology.

It is hoped that this integrative review of the literature will help other doctors and medical students to understand the diagnostic procedures regarding adrenal insufficiency induced by glucocorticoids, a subject that requires further studies, even though it is a pathology with a high potential for morbidity and mortality.

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