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Can Eosinophilia Serve as A Parameter for Adrenal Insufficiency?

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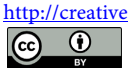

Abstract

Diagnosing adrenal insufficiency is challenging because its symptoms are nonspecific—such as nausea, fatigue and muscle weakness—overlap with those of many other medical diseases. Furthermore, in our hospital, cortisol and Adrenocorticotropic hormone (ACTH) must be outsourced to external laboratories, resulting in a 3-to-4-day delay, obtaining cortisol and ACTH test results takes time; Eosinophils are checked during routine blood tests, eosinophilia is only a "nonspecific clue" and can not replace confirmatory tests such as cortisol/ACTH testing.

Subject Areas

Emergency & Critical Care

Keywords

Adrenal Insufficiency, Eosinophilia, Cortisol, ACTH Stimulation Test

1. The Aim of a Narrative Clinical Review

Adrenal insufficiency is a rare but critical endocrine disorder characterized by insufficient glucocorticoid production -accompanied by mineralocorticoid deficiency—resulting from dysfunction of the adrenal glands, pituitary gland, or hypothalamus. Etiology of adrenal insufficiency include autoimmune diseases (such as Addison's disease), long-term steroid use, pituitary tumors, infections (such as tuberculosis), and the abrupt discontinuation of corticosteroids. The diagnosis of adrenal insufficiency can be difficult because its nonspecific symptoms—such as nausea, fatigue, muscle weakness, and cognitive impairment—overlap with those of many other medical diseases.

2. Clinical Presentation

Patients with adrenal insufficiency are frequently transported to the emergency

department in a state of shock, with hypotension being a primary clinical sign. Blood tests often reveal electrolyte abnormalities, such as hyponatremia and hyperkalemia, which are indicative of mineralocorticoid deficiency. Diagnosing an adrenal crisis is extremely difficult; early symptoms include nonspecific malaise, lethargy, loss of appetite, weight loss, and vomiting. Adrenal insufficiency is a disorder caused by a deficiency in steroid hormones (primarily cortisol) secreted by the adrenal glands. Because the symptoms are nonspecific, the condition is often overlooked.

These symptoms often progress gradually, and patients may simply feel "generally unwell." Another characteristic feature is that symptoms worsen during times of stress or upon contracting an infection.

In primary adrenal insufficiency (Addison's disease), pigmentation of the skin and mucous membranes may appear as a characteristic sign. This is caused by elevated levels of ACTH (adrenocorticotropic hormone) and is particularly noticeable around the joints and inside the mouth. In contrast, secondary adrenal insufficiency involves low ACTH levels, so pigmentation is not observed.

Recent studies report that approximately 80% of patients with adrenal insufficiency experience some form of psychiatric symptom (such as apathy, anxiety, or depression) prior to diagnosis [1]. These symptoms are frequently misdiagnosed as other conditions.

Diagnostic Criteria and Approach for Adrenal Insufficiency: Adrenal insufficiency is diagnosed through a combination of clinical symptom assessment and biochemical testing. The recommended diagnostic approach follows these steps:

a. Screening Tests

If suspicious symptoms are present, the following tests are performed: Early morning (8 - 9 AM) blood cortisol level, plasma ACTH concentration, serum electrolytes (Na, K), blood glucose level, peripheral blood test (presence or absence of eosinophilia).

An early morning blood cortisol level < 4 μg/dL indicates a high probability of adrenal insufficiency, while a level of 18 μg/dL or higher indicates normal adrenal function. Levels between 4 and 18 μg/dL cannot rule out the possibility of adrenal insufficiency [2], require further stimulation testing [3].

b. Stimulation tests for definitive diagnosis (Endocrine disorders)

The rapid ACTH stimulation test [4] is the most widely used method for the definitive diagnosis of adrenal insufficiency.

In our hospital, cortisol and ACTH must be outsourced to external laboratories, resulting in a 3-to-4-day delay; the inability to obtain immediate results makes it difficult to establish a definitive diagnosis on the spot. However, given the need for rapid intervention, it is crucial to suspect acute adrenal insufficiency based on the patient's medical history and clinical findings, and to initiate treatment immediately if there is a strong suspicion of the condition. Adequate adrenocortical function is important for surviving critical illness. Eosinophils are measured during routine blood tests, and abnormalities in eosinophil levels indicate various

pathological conditions, such as allergies, parasitic infections, autoimmune diseases, and certain types of cancer.

An increase in eosinophils has been known to be associated with Addison's disease for over 70 years [5]. Beishuizen *et al.* reported that 80% of suspected clinical cases of adrenal insufficiency had relative eosinophil counts of at least 3% of white blood cells [6], and some reports had shown that eosinophilia was associated with adrenal crisis. Two reports said that eosinophil counts had a tendency to increase before the diagnosis of adrenal insufficiency [7] [8]. Moreover, in cases of adrenal insufficiency, a positive CRP result was observed in a small number of cases, even in the absence of an apparent concurrent infection. CRP was synthesized by hepatocytes after acute inflammatory stimuli and was principally regulated at the transcriptional level by the cytokines interleukin-6 and interleukin-1β [9]. Adrenal insufficiency might activate these process; however, the underlying mechanism was not yet to be determined.

Moreover, the neutrophil-to-lymphocyte ratio (NLR) is a simple index calculated from the ratio of neutrophils to lymphocytes in the blood. It is attracting attention as a marker reflecting inflammatory and immune response and is used to assess prognosis and disease severity in conditions such as cancer and infectious disease. NLR has a well-known prognostic value and independently correlates with mortality in the general population and in several specific subsets of disease (sepsis, pneumonia, COVID-19). We used indicators of the severity and recovery of COVID-19 patients as criteria for deciding on hospitalization and discharge in our hospital. NLR could be used to assess the severity of various infections. Therefore, the purpose of this study is to evaluate whether eosinophilia can serve as a marker for the early detection of adrenal insufficiency.

3. Discussion

Peripheral blood eosinophilia is an absolute eosinophil count > 500 eosinophils/μL [10] and may be caused by allergic infection, inflammatory, autoimmune disorders, neoplastic disorders and metabolic conditions like adrenal insufficiency [11]. The association between eosinophilia and adrenal insufficiency, particularly in cases of Addison' disease, was first described by George W Thorn in the mid-20th century. He noted that when cortisol levels were low, the body was less able to suppress eosinophil production, consequently these patients had the characteristic high value of eosinophils 5. While Thorn's work progressively advanced the understanding of the link between eosinophils and adrenal insufficiency, establishing that an increase in eosinophils served as an indirect indicator of adrenal insufficiency.

From the point of my clinical experience, shocked patients produced lots of cortisol. Cortisol suppressed the eosinophil count. Therefore, patients with severe shock had reduced numbers of eosinophils (frequently zero). But, in cases of shock accompanied by eosinophilia, we should not immediately diagnose adrenal insufficiency. After excluding other common causes, eosinophilia in shocked pa-

tients should raise suspicion of adrenal insufficiency. Eosinophilia was only a "non-specific clue" and could not replace confirmatory tests such as cortisol/ACTH testing.

But, the mechanism remains complex and multifactorial.

Eosinophilia in adrenal insufficiency is primarily caused by cortisol deficiency. Cortisol normally suppresses eosinophil production and promotes apoptosis [12]. This eosinophilia typically resolves with appropriate hormone replacement therapy; when hydrocortisone is administered to patients with adrenal insufficiency, eosinophil counts return to normal within 24 hours. However, in cases of adrenal insufficiency, blood sampling for cortisol and ACTH is essential prior to the administration of hydrocortisone. Blood test results obtained 2 or 3 days later are useful for assessing the severity of adrenal insufficiency. Although the link between eosinophils and adrenal function is often overlooked, a full understanding of this relationship enables earlier recognition of potentially life-threatening adrenal insufficiency and timely treatment. In adrenal insufficiency, the adrenal glands fail to produce sufficient cortisol. Cortisol is a glucocorticoid hormone that plays a crucial role in regulating eosinophils; a lack of cortisol leads to eosinophilia. Cortisol normally inhibits the release of interleukin-5 (IL-5) and other cytokines that stimulate eosinophil production and survival [13]. Furthermore, cortisol reduces eosinophil production by suppressing lymphocyte activity [14]. It also promotes the sequestration of eosinophils in lymphoid tissue and facilitates their removal from circulation [15]. Eosinophil levels rise in adrenal insufficiency because these regulatory mechanisms are absent. In the diagnosis of adrenal insufficiency, an increase in eosinophils was detected as an abnormal value in blood tests—appearing prior to the onset of clinical symptoms such as hypotension—suggesting its importance as an early indicator for assessing adrenal function.

But, eosinophilia was nonspecific supportive finding requiring clinical assessment and confirmatory endocrine testing.

4. Conclusion

In the diagnosis of adrenal insufficiency, when cortisol and ACTH cannot be measured promptly, an increase in eosinophils appeared to be an important indicator for the early assessment of adrenal function. The association between eosinophilia and adrenal insufficiency is often overlooked, leading to potential delays in diagnosis. Early understanding of the relationship between eosinophils and adrenal insufficiency leads to timely treatment and improved patient's prognosis.

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Conflicts of Interest

The author declares no conflicts of interest.

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