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Adrenal insufficiency in children with sepsis

Frequência de insuficiência adrenal em crianças com sepse

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ABSTRACT

Objective: To determine the frequency of adrenal insufficiency in children diagnosed with sepsis that were staying in pediatric intensive care units and to establish the association between adrenal function and the use of vasoactive drugs, mechanical ventilation time and mortality.

Methods: A cohort-designed study was conducted to assess the incidence of adrenal insufficiency in children aged 29 days to 12 years who were diagnosed with sepsis using the adrenocorticotropic hormone (ACTH) stimulation test.

Results: Thirty-nine children were included in the study. The frequency of adrenal insufficiency was 30.7% (12 patients). Children with adrenal insufficiency had an increased need for vasoactive drugs as well as longer mechanical ventilation times; however, the differences were not statistically significant. A Kaplan-Meier curve indicated lower survival rates among the adrenal insufficiency children, but the differences were not statistically significant (p = 0.1263). No differences were identified between the adrenal sufficiency and adrenal insufficiency groups in regards to mechanical ventilation time, use of vasoactive drugs, infection type and chronic disease.

Conclusion: This study determined the frequency of adrenal insufficiency in children with sepsis and its relationship to increased mortality within the first 28 post-admission days. No statistically significant association was found between adrenal insufficiency and mechanical ventilation time or the use of vasoactive drugs.

Keywords: Sepsis; Adrenal insufficiency; Corticotropin-releasing hormone; Vasoactive drugs; Children

INTRODUCTION

The hypothalamic-pituitary-adrenal axis is responsible for homeostasis and is activated under stressful conditions, such as severe disease, trauma, anesthesia and surgery, leading to increased serum cortisol levels. This axis is mostly activated by the release of inflammatory cytokines. The mobilization of endogenous steroid stocks is responsible for the maintenance of the vascular tonus and endothelial integrity, control of vascular permeability and distribution of total body water, in addition to adrenergic receptor sensitization. Continuous axis stimulation leads to the exhaustion of cortisol stocks and adrenal insufficiency.[1]

Total adrenal insufficiency is rare, with an incidence between 2 and 3% among critically ill patients, and its primary triggering events are hemorrhage and post-traumatic tissue destruction.[2] Secondary dysfunction occurs after cortisol stocks are exhausted. In addition, secondary dysfunction can also be caused by peripheral resistance to adrenocorticotropic hormone

(ACTH) Sepsis is one of the most common total adrenal insufficiency triggering events. Other clinical conditions may contribute to partial adrenal failure, such as autoimmune adrenalitis, disseminated tuberculosis, metastasis and partial hemorrhagic gland destruction.[2]

The main clinical features leading to adrenal insufficiency are related to hemodynamic conditions, with symptoms typically associated with hypovolemic shock, reduced afterload, myocardial depression and increased peripheral vascular resistance, or typical hyperdynamic shock with increased cardiac output and reduced peripheral vascular resistance. Under such conditions, arterial hypotension is the most common clinical outcome.[3] Baseline cortisol is widely variable during severe symptom manifestations, and its fluctuation is associated with a poor prognoses.

The baseline cortisol measurement has been widely used to diagnose adrenal insufficiency, both in experimental models and clinical trials. The findings of previous studies indicated that increased serum cortisol is a response to trauma and severe disease. However, as the variables impacting the measurement of baseline cortisol levels and the differences between free and globulin-bound forms have become known, new adrenal function assessment methods have been examined. The results of several studies, including many multicenter trials, indicate that the most trustworthy way to evaluate adrenal insufficiency is the adrenocorticotropic hormone (ACTH) stimulation test. The use of this test allows for not only the diagnosis of adrenal insufficiency but also the adrenal insufficiency status to be rated and quantified prior to deciding the appropriate therapeutic approach.[4,5]

ACTH acts directly on the adrenal cortex to promote cortisol secretion. The ACTH stimulation test represents an alternative to the diagnosis of secondary adrenal insufficiency, with different methodologies in accordance with dosage.[6] Lower ACTH doses (e.g., one microgram) are more sensitive.[7]

Therefore, the main objectives of this study were to determine the frequency of adrenal insufficiency in children diagnosed with sepsis who were staying in pediatric intensive care units and to establish the association between adrenal function and the use of vasoactive drugs, mechanical ventilation time and mortality.

METHODS

During the first phase of the study, children with a sepsis diagnosis were selected in accordance with the presence of signs representing a systemic inflammatory response syndrome in association with clinical or laboratory evidence of an infection, all in accordance previously published criteria.[8] The following were considered symptoms of organ dysfunction: serum lactate > 2.2 mmol/L, urinary output < 1 mL/kg/h, base excess < -3, partial oxygen pressure/inspired oxygen fraction ratio (PaO_2/FiO_2) < 300 and altered consciousness level. Arterial hypotension was defined as a systolic blood pressure (SBP) below the 5th age percentile, i.e., SBP < (70 mmHg + 2 times the age in years). The sample included children with the following criteria: an age range of 29 days to 12 years, clinical and laboratory criteria for sepsis and admission to the pediatric intensive care unit of Hospital Regional do Norte do Paraná from August 2004 to July 2005. This was a cohort-designed study.

A systemic inflammatory response was diagnosed by fever or hypothermia, tachycardia, tachypnea or hyperventilation and white blood cell changes, including absolute leukocyte counts and ratio of immature cells in the peripheral blood for all patients in the study. Clinical tests, chest X-rays, urinalysis from single sample, blood chemistry, cytology and the culturing of specific sites were used to evaluate and diagnose infection.

Newborns were excluded from the patient sample. In addition, exclusion criteria also included known hypothalamus-pituitary-adrenal axis abnormalities; chronic use of corticosteroids, phenytoin, and phenobarbital; recent use of rifampicin or etomidate; and diagnosis of disseminated tuberculosis or acquired immunodeficiency syndrome (AIDS).

After patient selection, serum cortisol was evaluated by removal of two mL of blood into a non-anticoagulant bottle. The collection was conducted by the first author for all patients. Next, ACTH stimulation was conducted using a one-microgram dose of intravenous adrenocorticotropic hormone followed by a new cortisol assessment 60 minutes post-stimulation. Withdrawn blood was then centrifuged, frozen and stored (at -4ºC) for later analysis. Cortisol levels were evaluated by radioimmunoassay. Sampling was conducted within the first 24 hours post-admission to the intensive care unit in cases where sepsis was the admission diagnosis or within the first 24 hours post-sepsis diagnosis when sepsis developed during the hospital stay.

A patient was considered to have adrenal insufficiency when the post-ACTH stimulation cortisol level increased by less than 9 mcg/dL over the baseline value.[9] This value for adrenal insufficiency diagnosis was based on a study by Annane et al.[4]

We analyzed the rate of adrenal insufficiency in

the study sample and the patient clinical outcomes as compared to patients with normal adrenal function. Vasoactive drug requirements and lengths of use, mechanical ventilation needs and times, laboratory evidence of impaired cardiac output using serum lactate dosage and demographics were all analyzed. In addition, the overall group mortality within 28 days post-admission and the total length of stay until the outcome (i.e., death or discharge from the intensive care unit) were assessed.

The demographics and clinical features were analyzed by comparing children with and without an adrenal insufficiency diagnosis. The numerical variables were assessed for their normal distribution (Shapiro-Wilk test). Variables that were determined to not have a normal distribution are presented as medians and quartiles. The categorical variables are presented as absolute and relative frequencies. The Mann-Whitney test was used to compare the numerical group variables. The association between the primary endpoint (with or without adrenal insufficiency) and categorical variables were assessed using the Fisher exact test. In addition, the survival curve of the groups was compared using a Kaplan-Meier plot. The statistical significance level was established at 5% ($p \leq 0.05$). The statistical analyses were conducted using the Statistical Package for Social Science (SPSS, version 11.5).

This study was approved by the ethics committee of Hospital Universitário Regional do Norte do Paraná (EC 099/14). The legal representatives of the patients were appropriately informed about the study and signed a written informed consent form.

Table 1 - Patient demographics

	With adrenal insufficiency N (%)	Without adrenal insufficiency N (%)
Less than 1 year-old	2 (16.7)	16 (59.3)
1 to 2 years-old	3 (25.0)	4 (14.8)
More than 2 years-old	7 (58.3)	7 (25.9)
Male	6 (50.0)	14 (51.9)
Female	6 (50.0)	13 (48.1)

RESULTS

During the study period, 39 children were enrolled and divided into three age ranges. Eighteen patients were less than one year-old, seven were between one and two years-old and fourteen were above two years-old. These groups had similar demographic data, such as gender and age range (Table 1). When the sample was divided into two or fewer years-old children and more than two years children, a larger proportion of the older children had adrenal insufficiency, but the difference was not statistically significant ($p = 0.057$). Of the 39 children, 20 were male and 19 female.

Moreover, 12 (30.7%) had tests indicative of adrenal insufficiency. The median baseline cortisol values were 17.2 mcg/dL. The post-ACTH cortisol values were 32.4 mcg/dL, and the median post-stimulation response was 11.7 mcg/dL. Among the 12 children with adrenal insufficiency, six were male and six female.

The overall mortality was 25.6% (10 patients). An analysis of the outcomes suggests that death was more common in children with adrenal insufficiency than among normal functioning children; however, this difference was not statistically significant ($p = 0.13$). The analysis of 28-day mortality indicated a significantly increased death rate for the adrenal insufficiency group ($p = 0.043$, Table 2). The Kaplan-Meier curve also indicated lower survival rates among adrenal insufficiency children, but the difference was not statistically significance ($p = 0.1263$) (Figure 1).

Serum lactate tissue perfusion testing demonstrated no significant difference between the groups ($p = 0.654$). In addition, no differences were found for chronic disease or type of infection. The duration of circulatory support with catecholamines was longer in adrenal insufficient children but did not reach statistical significance ($p = 0.061$). The mechanical ventilation time was not statistically different between the groups ($p = 0.374$).

Table 2 - Mortality according to adrenal insufficiency diagnosis at admission

	With adrenal insufficiency N (%)	Without adrenal insufficiency N (%)	p value
Death before 7 days post-admission	0 (0)	1 (20)	0.692
Death before 28 days post-admission	5 (100)	3 (60)	0.043
Death after 28 days post-admission	0 (0)	1 (20)	0.130
Total	5 (50)	5 (50)	

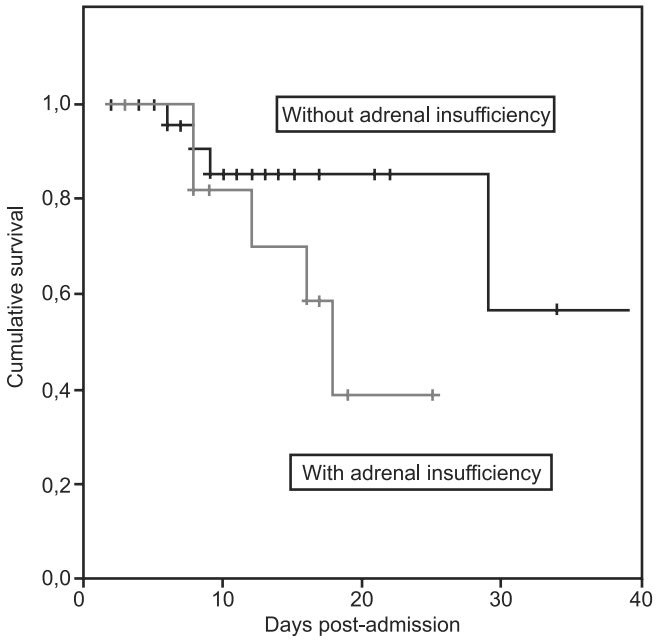

Figure 1 – The Kaplan-Meier curve comparison of survival between the groups: children with and without adrenal insufficiency (p = 0.1263).

DISCUSSION

Secondary adrenal insufficiency is common is children with septic shock and other organ stress conditions.[10-13] In such conditions, the hypothalamus-pituitary-adrenal axis is activated, initially leading to increased free cortisol.[14] Next, the entire axis is exhausted and peripheral cortisol resistance leads to the development of adrenal insufficiency.[15-17] The related adrenal dysfunction incidence is variable and depends on both the sample profile and the diagnosis criteria.[18,19]

The results of this study confirm the existence of adrenal insufficiency in children suffering septic shock. These results are concordant with the results found by Pizarro et al. using similar diagnosis methods. They found an incidence of 44% in a 57-child sample.[20]

A dynamic test was performed using a low ACTH dose (one microgram). A study by Annane et al.[4] was used as the model for adrenal function assessment in our sample (9 mcg/dL response). This criterion was also used by Marik et al.[7] However, a 250-microgram ACTH dose was used in a study by Pizarro et al.[20] Dynamic ACTH testing has been used in most of the studies assessing adrenal insufficiency prevalence and incidence, both in adults and children.[21-24] In addition, other diagnostic methods are available, such as baseline cortisol, free cortisol and serum ACTH dose measurement.

In a study by Kleijn et al., an assessment of children with meningococcal disease found lower cortisol and ACTH values than non-diseased children.[6] Marik et al. examined baseline cortisol levels to diagnose adrenal insufficiency, in addition to a dynamic ACTH test. The respective insufficient frequencies were 61% for baseline values and 22% after the dynamic test.[7]

In this study, the 28-day overall mortality was 58%, with a significantly larger number of adrenal dysfunction patients dying ($p < 0.001$). The Kaplan-Meier curve also indicated lower survival likelihood for patients with adrenal function impairment. However, this difference was not significant. An analysis of the clinical outcome indicated no association between the diagnosis of adrenal insufficiency and length of hospital stay or mechanical ventilation time. These results are different from other studies. The vasoactive drug-use duration was longer in children with adrenal insufficiency, but the difference was not statistically significant. In a study by Hatherill et al. of a similar sample, a higher adrenal insufficiency (52%) frequency was found, along with increased vasoactive drug-use duration requirements in the adrenal insufficiency group. In addition, the adrenal insufficiency group had a worsened prognosis. In concordance with our results, Hatherill et al. found no statistically significant association between adrenal insufficiency and mechanical ventilation time.[10]

In a study by Loisa et al.,[5] after analyzing the adrenal function of 41 patients, the deficiency group was found to have a longer stay in the intensive care unit and remain longer under mechanical ventilation; both differences were significant. Adrenal insufficiency, along with higher ACTH doses, was diagnosed by these authors in six patients. In both studies, unfavorable clinical outcomes were related to disease severity or refractory septic shock independent of adrenal function.

In our study, admission and prognostic scores were analyzed, but no associations with adrenal function or clinical outcome were found. In addition, the timing of the dynamic ACTH test was debated. This patient sample was conducted within the first 24 hours post-admission or post-sepsis diagnosis. This was both arbitrary and punctual, as impairment of adrenal function may take place at other times during hospitalization and sepsis progression. New methodologies should be developed for systematic adrenal function assessment and determination of the optimal time for dynamic ACTH testing.

In this study, adrenal insufficiency was shown to be common in septic patients. However, when compared with the findings of other authors, our frequency was lower, and no association with the clinical outcome was found. The small sample size was limiting, as was the unavailability of pre-admission assessments. Additional studies with larger sample sizes that would allow improved diagnostic criteria are warranted so are clinical trials to assess the treatment of adrenal insufficiency in pediatric patients.

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RESUMO

Objetivo: Determinar a frequência de insuficiência adrenal em crianças com diagnóstico de sepse internadas em unidades de terapia intensiva pediátrica e estabelecer a associação entre a função adrenal e a necessidade e tempo de utilização de drogas vasoativas, tempo de ventilação mecânica e mortalidade.

Métodos: Estudo de coorte destinado a avaliar a incidência de insuficiência adrenal em crianças com idade de 29 dias a 12 anos e diagnóstico de sepse por meio do teste de estímulo com ACTH.

Resultados: Foram incluídas 39 crianças no estudo. A freqüência de insuficiência adrenal foi de 30,7%, totalizando 12 pacientes. Observou-se maior necessidade de drogas vasoativas, bem como no tempo de ventilação mecânica em crianças com insuficiência adrenal, porém sem significância estatística. A curva de Kaplan-Meyer mostrou menor sobrevivência no grupo de crianças com insuficiência adrenal, sem significância estatística (p = 0,1263). Não houve diferenças entre os grupos com e sem insuficiência adrenal quando avaliados tempo de ventilação mecânica, necessidade de drogas vasoativas, tipo de infecção e presença de doenças crônicas.

Conclusão: O estudo determinou a frequência de insuficiência adrenal em crianças com sepse e sua relação com maior mortalidade nos primeiros 28 dias de internação. Não se encontrou significância na associação entre insuficiência adrenal e tempo de ventilação mecânica ou necessidade de drogas vasoativas.

Descritores: Sepse; Insuficiência adrenal; Hormônio liberador de corticotropina; Vasodilatadores; Criança

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