Rev. Inst. Med. trop. S. Paulo
48(6):333-336, November-December, 2006

ADRENAL FUNCTION IN 23 CHILDREN WITH PARACOCCIDIOIDOMYCOSIS

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SUMMARY

Adrenal involvement by *Paracoccidioides brasiliensis* was described at necropsies and in many clinical studies, but only in adults. Therefore, the aim of this study was to evaluate adrenal function in children with paracoccidioidomycosis.

Twenty-three children with the systemic form of paracoccidioidomycosis were evaluated and divided in two Groups: Group A (n = 8) included children before treatment and Group B (n = 15) children after the end of treatment. Plasma cortisol (basal and after ACTH test), ACTH, renin activity, aldosterone, sodium and potassium were measured. They were within normal range in all cases, except for renin activity and aldosterone, which were elevated in some cases. Group A patients showed basal and post-ACTH cortisol levels significantly greater than Group B patients. The results showed that adrenal function was not compromised in these children with paracoccidioidomycosis.

KEYWORDS: Paracoccidioidomycosis; *Paracoccidioides brasiliensis;* Children; Adrenal; Cortisol and ACTH.

INTRODUCTION

Paracoccidioidomycosis (PCM) is a chronic granulomatous disease caused by the fungus *Paracoccidioides brasiliensis*. It is the most common systemic mycosis in South America, especially in the Southern and Southeastern regions of Brazil[3]. The clinical form of PCM varies from a self-limited infection to a severe, progressive, and sometimes-fatal disease, which involves pulmonary and extra pulmonary tissues[8]. The acute form is characterized by systemic lymphoadenopathy, hepatosplenomegaly, bone marrow dysfunction, and a great impairment of patient's general condition, especially in young persons. The chronic form presents progressive pulmonary or extra pulmonary (mucocutaneous, lymph nodes, adrenal glands, intestine, bone, etc) manifestations[13]. Previous studies found impairment of adrenal function in a high percentage (10 to 44%) of patients with PCM[2,4,5,11,13,15,16,19]. These studies used different methods and criteria to diagnose adrenal dysfunction; some of them were done before PCM treatment and others after, and all involved only adult patients. Therefore, the aim of this study was to evaluate adrenal function in children with PCM.

PATIENTS AND METHODS

Twenty-three children with the acute form of PCM were included in this study, eight of them (Group A) without treatment and 15 (Group B) after the end of treatment. These patients are part of a cohort of children with PCM previously described[18]. The study was conducted from January to August 2002. PCM was confirmed by lymph node, skin or bone biopsy in all children. All of the children were treated with the association of sulfamethoxazole-trimethoprim, at a dosage of 8 mg/kg/day (trimethoprim). No other drug was used. Salt ingestion was not controlled in these patients, who were evaluated regardless of the presence of any symptoms and/or signs suggestive of hypocortisolism. After an overnight fast, a morning baseline blood sample was collected, at recumbent position, to measure plasma cortisol, ACTH, renin activity, sodium (Na) and potassium (K). ACTH 1-24 (0.25 mg of tetracosactrin; Organon) was them given as an IV bolus, and another sample for cortisol measurement was obtained 60 min after the injection. Cortisol and ACTH were determined respectively by solid-phase, competitive chemiluminescent enzyme immunoassay and solid-phase, two-site sequential chemiluminescent immunometric assay (DPC Immulite, USA); renin activity (PRA) by radioimmunoassay of generated angiotensin I (DiaSorin, USA), aldosterone by radio immunoassay (DPC RIA, USA), and Na and K by flame spectrophotometer. The intra- and interassay coefficients of variation were respectively, 6.2% and 7.3% for cortisol; 3.1% and 5.1% for ACTH; 4.6% and 5.6% for PRA; and 6.5% and 8.1% for aldosterone. The normal values ranged from 5.0 to 25.0 µg/dL for cortisol; zero to 46.0 pg/mL for ACTH; 0.15 to 2.33 ng/mL/h for PRA; 10.0 to 310.0 pg/mL for aldosterone; 132 to 145 mEq/L for Na; and 3.1 to 5.1 mEq/L for K. According to MENDONÇA[12], the diagnostic criteria for primary glucocorticoid insufficiency was basal cortisol below 5.0 µg/dL and ACTH above 46 pg/mL or cortisol increment after ACTH test below 7.0 µg/dL or absolute value of cortisol after ACTH test below 15.0 µg/dL; and for mineralocorticoid insufficiency was low levels of Na and aldosterone and high levels of K and PRA.

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A database was constructed in order to obtain the frequency distribution of the studied variables, using the software *SPSS for Windows 10.0*. The significance of the differences in some laboratory tests (basal and post-stimulus cortisol and ACTH) was evaluated using the Mann-Whitney (non-parametrical test for non-related samples) tests. These results are shown as box and whisker plots. A p value of 0.05 was considered significant.

The Ethics Committee of the School of Medicine of UNICAMP approved the study and a written informed consent was obtained from at least one parent.

RESULTS

No patients presented symptoms or signs of hypocortisolism. Glucorticoid function was normal in all patients, and the increase in serum cortisol levels in response to ACTH stimulation was adequate (Table 1). Although all patients had normal cortisol values, patients of Group A presented basal and post-ACTH cortisol significantly greater than patients of Group B (Mann-Whitney test, $p < 0.01$; Fig. 1). Similar concentrations of ACTH were seen in both Groups.

Twelve patients showed aldosterone levels above the normal limits and two patients showed elevated renin activity; aldosterone and rennin activity were elevated in only one patient. Serum sodium and potassium levels were within normal range in all patients (Table 1).

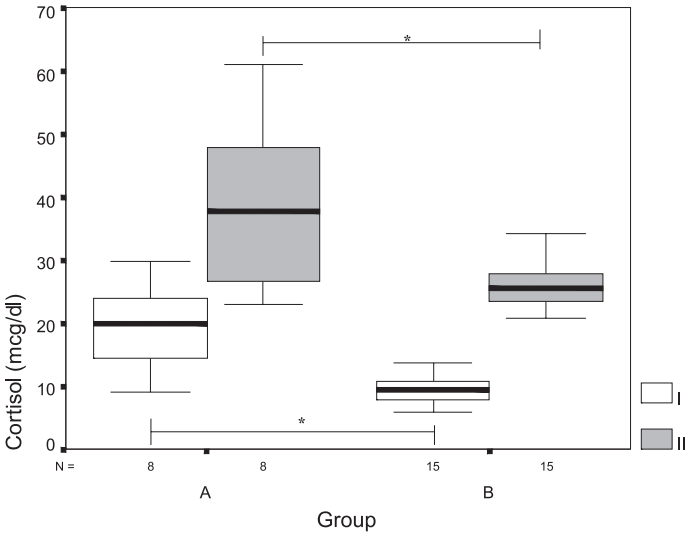

Fig. 1 - Box-plot of basal cortisol (I) and cortisol post-ACTH (II) in 23 children with PCM according to Group A and Group B. Mann-Whitney test (* $p < 0.01$).

Table 1
Adrenal function data from 23 children with PCM

Patient	F 1	F 2	ΔF	ACTH	PRA	Aldosterone	Na	K
1	29.7	61.0	31.3	22.6	17.5	25	135	3.9
2	24.2	50.0	25.8	30.1	25.7	347	136	4.0
3	19.9	39.7	19.8	17.1	4.4	58	140	3.9
4	17.8	28.7	10.9	40.7	3.5	369	143	4.3
5	23.7	45.8	22.1	27.0	5.1	48	138	3.7
6	19.9	35.5	15.6	10.0	1.9	110	140	3.8
7	9.0	24.3	15.3	28.2	3.7	67	138	3.6
8	11.2	22.9	11.7	20.0	2.0	293	139	4.1
median Group A	19.9	37.6	17.7	24.8	4.04	88.39	138	3.9
9	10.0	26.8	16.8	28.1	1.2	103	138	4.2
10	7.0	28.5	21.5	30.0	2.1	98	142	3.7
11	10.5	27.0	16.5	23.0	2.9	106	137	4.8
12	8.8	34.1	25.3	36.3	1.4	55	140	3.9
13	5.8	24.5	18.7	21.0	2.8	30	141	4.1
14	13.7	33.2	19.5	33.3	5.5	88	135	3.7
15	9.3	21.9	12.6	23.0	1.5	103	139	4.1
16	13.1	27.0	13.9	19.8	1.9	76	137	3.9
17	9.2	25.4	16.2	11.2	1.1	42	141	4.2
18	7.4	24.2	16.8	23.9	1.7	165	137	4.3
19	5.8	21.0	15.2	16.1	5.6	138	136	3.9
20	8.1	20.8	12.7	20.5	2.7	35	135	4.0
21	11.0	28.8	17.8	12.9	1.9	202	139	4.2
22	9.3	24.2	14.9	10.1	2.9	33	136	3.9
23	12.0	22.8	10.8	30.6	0.9	137	142	4.0
median Group B	9.3	25.4	16.5	23.0	1.92	87.7	138	4.0

Group A = patients 1 to 8; Group B = patients 9 to 23; F = cortisol; ΔF = cortisol increment; 1 = basal; 2 = 60' after ACTH test. Reference values: cortisol 5.0 to 25.0 µg/d, ACTH zero to 46.0 pg/mL, PRA 0.15 to 2.33 ng/mL/h, aldosterone 10.0 to 310.0 pg/mL, Na 132 to 145 mEq/L, K 3.1 to 5.1 mEq/L.

DISCUSSION

Glucocortid function was considered normal in all patients, with an adequate response to ACTH stimulation, which can be due to the short time between symptoms and the onset treatment. In adult population with PCM, some authors have demonstrated that adrenal involvement depends on the amount of time between the first symptoms and the onset of treatment - the greater the delay, higher is the frequency of adrenal involvement[6]. Although this is not a rule[4], the short time of disease before treatment could explain our results.

The use of three laboratorial tests (plasma ACTH and pre and post stimulus cortisol) elevated the sensitivity to recognize glucocorticoid insufficiency; however, the high dose of ACTH used in this work could reduce that, especially in patients with a low cortisol reserve. Nowadays, a lower dose of ACTH (1 µg) is being used as a sensitive test in patients with subtle adrenal dysfunction, which is considered to be the test of choice in the evaluation of adrenal function in pituitary diseases[20]. Lower doses are considered to be more physiological, avoiding a hyper-stimulus, and the results obtained are similar to hypoglycemia induced by insulin or a great physical stress[14]. There are not enough data on the use of low doses of ACTH in the evaluation of primary adrenal dysfunction. Some authors have demonstrated similar results with low and standard doses (1 and 250 µg), suggesting that a lower dose of ACTH is enough to diagnose sub clinical adrenal insufficiency[10,21]. Other authors have found a greater frequency of primary adrenal dysfunction in patients with Acquired Immunodeficiency Syndrome using low doses in comparison to other studies that used standard doses[23]. In this study we demonstrated adrenal reserve in all patients, but we don't know if the results would be the same with a low dose of ACTH.

We argue that recovery of the adrenal function after treatment occurred in patients of Group B, as described in adult population with PCM[1,7]. It is not possible to rule out this hypothesis, since all children were seen monthly in the hospital and none of them presented symptoms or signs of hypocortisolism, although symptoms and/or signs of adrenal dysfunction like asthenia, weight loss or anorexia are vague and non-specific, misleading this suspicion.

Although all patients had normal cortisol values, Group A showed higher levels of cortisol (basal and post-ACTH) than Group B. Like in adult population with PCM or other infectious diseases, these results could be due to the stress of the acute phase of this disease[4]. If it was true, a high level of ACTH would be expected, but this fact did not occur. In the acute phase of the infection, direct action of inteleukin-6 in the adrenal gland stimulates local steroidogenesis without activation of the hypothalamus - pituitary axis. In this study high levels of cortisol and normal levels of ACTH in both Groups suggest the occurrence of local steroidogenesis[9,17].

Some patients presented high levels of renin activity and/or aldosterone, but all had sodium and potassium within normal range. These data were not compatible with mineralocorticoid insufficiency, and it can be explained by hypoalbuminemia, which is common in these PCM patients[18], or different level of dietary sodium[22], which was not controlled in this study. The relationship between hypoalbuminemia and cases with more severity and/or more time of disease was also not established in these cases.

In conclusion, the adrenal function was not compromised in these children with PCM.

RESUMO

Função adrenal em 23 crianças com paracoccidioidomicose

O acometimento adrenal pelo *Paracoccidioides brasiliensis* é descrito em necropsias e em estudos clínicos, mas apenas em adultos. Portanto, o objetivo deste estudo foi avaliar a função adrenal em crianças com paracoccidioidomicose.

Vinte e três crianças com forma sistêmica de paracoccidioidomicose foram avaliadas e divididas em dois grupos: Grupo A (n = 8) pacientes antes de iniciar o tratamento e Grupo B (n = 15) pacientes após o termino do tratamento. Dosagens plasmáticas de cortisol (basal e após teste com ACTH), ACTH, atividade de renina, aldosterona, sódio e potássio foram realizadas. Estas dosagens foram normais em todos os casos, com exceção da atividade da renina e da aldosterona que foram elevadas em alguns casos. Os pacientes do Grupo A mostraram valores de cortisol basal e após-ACTH significativamente maiores que os do Grupo B. Os resultados demonstraram que a função adrenal não foi comprometida neste grupo de crianças com paracoccidioidomicose.

ACKNOWLEDGMENTS

To Profa. Dra. Andrea Trevas Maciel Guerra, for reviewing the English text.

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Received: 9 September 2005
Accepted: 27 June 2006