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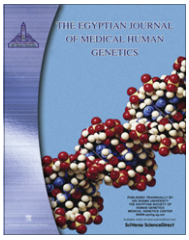

ORIGINAL ARTICLE

Hepatoadrenal syndrome in Egyptian children with liver cirrhosis with and without sepsis

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KEYWORDS

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Abstract The similarities between septic shock and liver failure led to the proposal of the term hepatoadrenal syndrome. Adrenal insufficiency has been demonstrated in patients with severe liver disease irrespective of the presence of sepsis. The objective of this study was to evaluate children with liver cirrhosis for the presence of adrenal insufficiency especially during critical illness. This pilot study was designed to evaluate adrenal function for 24 children with liver cirrhosis of various etiologies by measuring basal cortisol level and measuring the peak level after 30 min of short low dose ACTH stimulation test. They were categorized in two groups; group 1 included 12 patients with sepsis and group 2 included 12 patients without sepsis. It was found in this study that no one of patients of group1or group 2 had absolute adrenal insufficiency; however 11 patients, 8 (66.6%) of group 1 and 3 patients (25%)of group 2 had relative adrenal insufficiency (RAI) as the increment detected in cortisol level after stimulation was < 9 μgm/dL. There was significantly higher incidence of RAI in group 1 compared to group 2 ($P = 0.05$). Most of patients with RAI (72.7%) were categorized as having Child–Pugh C liver cirrhosis. The presence of ascites, high temperature, high C reactive protein, neutrophilia, high ALT, AST, high total bilirubin, prolonged INR and lower albumin were all risk factors associated with the occurrence of RAI. Survival rate in patients with normal adrenal function (92%) was significantly better than in patients with RAI (27%) ($P = 0.02$). It was concluded from this study that a high incidence of relative adrenal insufficiency was found in children with liver cirrhosis. It was more common in the presence of sepsis, related to the degree of liver cirrhosis and carried a bad prognosis.

1. Introduction

Adrenal failure is emerging as an important cause of excess morbidity and mortality in critically ill patients [1]. Activation of the hypothalamic–pituitary–adrenal axis with the release of cortisol is an essential component of the general adaptation to illness and stress and contributes to the maintenance of cellular and organ homeostasis [2,3].

As liver failure and sepsis are both associated with increased circulating levels of endotoxin and proinflammatory

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mediators and reduced levels of apoprotein-ll, high-density lipoprotein, adrenal failure was proposed to occur in patients with liver disease [4]. Liver failure is well recognized to cause renal (hepatorenal syndrome) and pulmonary (hepatopulmonary syndrome) disease. Since high incidence of adrenal failure in critically ill patients with liver disease has become evident [5,6]; consequently the term hepatoadrenal syndrome has been introduced [7].

The reported prevalence of adrenal insufficiency varies widely in critically ill patients, depending on the population of patients studied and the diagnostic criteria. During the last few years recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients have been reported. The term relative adrenal insufficiency (RAI) or critical illness-related corticosteroid insufficiency (CIRCI) is defined as inadequate cellular corticosteroid activity for the severity of the patient's illness irrespective of the basal cortisol level [8].

The objective of this study was to evaluate children with liver cirrhosis for the presence of adrenal insufficiency especially during critical illness.

2. Subjects and methods

This pilot study included 24 children with liver cirrhosis of different etiologies attending the Pediatric Hepatology Clinic, Children's Hospital, Faculty of Medicine, Ain Shams University. The diagnosis of cirrhosis was based on clinical (firm hepatomegaly, splenomegaly, portal hypertension) and histopathological data (disturbed architecture, grade 6 fibrosis, nodules). They were classified into 2 groups; group 1 included 12 children with liver cirrhosis who were admitted to the inpatient ward because of sepsis. Group 2 included 12 children with liver cirrhosis without sepsis. The study was conducted in the period from November 2009 to June 2011. It was performed according to the recommendations of the Ethics Committee of Children's Hospital, Ain Shams University. An informed consent was obtained from the children's guardians.

2.1. Exclusion criteria

- Children on steroids or with history of steroids intake during the last six months as children with autoimmune hepatitis or recently operated biliary atresia.

Diagnostic criteria of sepsis were based on the international sepsis definition conference [9] which includes documented or suspected infection plus other data including: fever (core temperature > 38.3 °C), hypothermia (core temperature < 36 °C), leukocytosis (WBC count > 12,000/mm^3), leukopenia (WBC count < 4000/mm^3), normal WBC count with >10% immature forms, plasma C-reactive protein(CRP) > 2 SD above the normal value.

All the included patients were subjected to clinical evaluation laying stress on age, sex, etiology of liver cirrhosis, Child–Pugh classification, source of infection, body temperature, and the presence of ascites. The following laboratory investigations were done: complete blood count CBC with differential count, C-reactive protein (CRP), liver function tests [total and direct bilirubin, international normalized ratio (INR), and serum albumin], liver enzymes [alanin aminotransferase (ALT), aspartate aminotransferase (AST)].

The adrenal function of all patients was assessed by low dose test (LDT) through measuring the basal level of cortisol at 10 am; then a 1 μg of synthetic ACTH analogue through IV access was given for stimulation of the adrenal gland, after 30 min a second blood sample was obtained for estimation of increment of cortisol level [10].

A Basal cortisol levels < 7 μg/dL and/or peak cortisol level at 30 min after stimulation < 18 μg/dL were used to define adrenal insufficiency. The diagnosis of relative adrenal insufficiency was considered if the increment in cortisol level was < 9 μg/dL 30 min after stimulation [11,12].

2.2. Statistical analysis

Descriptive and analytical statistics were performed on IBM-compatible computer by using SPSS 13.0 software package. Graphic presentation of data was performed by using Excel 2003 software package. Data were presented in the form of mean ± SD. Categorical data were presented in the form of number and percentage.

Comparisons between various studied groups were performed by using Mann Whitney U test or *t*-test. Associations between categorical parameters were performed by using chi square test (χ^2 value) or Fisher's exact test. Power of significance (probability): $P > 0.05$ is not significant. $P < 0.05$ is significant.

3. Results

Children of group 1 had liver cirrhosis due to biliary atresia ($n = 8$), progressive familial intrahepatic cholestasis ($n = 2$), Caroli disease ($n = 1$), and tyrosienemia ($n = 1$). More than half of this group scored as Child–Pugh C (58.3%) which was statistically more frequent than in group 2 ($P = 0.05$). Patients of group 1 were hospitalized for sepsis due to ascending cholangitis ($n = 4$), pneumonia ($n = 3$), infected hepatic cysts ($n = 2$), gastroenteritis ($n = 2$), and spontaneous bacterial peritonitis ($n = 1$). Blood culture was done for 7 patients and revealed no growth in 3/7, *Klebsiella* in 2/7, and *Staphylococcus aureus* in 1/7 and *Escherichia coli* in 1/7. Patients received intravenous antibiotics either according to culture and sensitivity or broad spectrum antibiotics. Albumin and diuretics were given if indicated in addition to other supportive measures.

Children of group 2 had liver cirrhosis due to biliary atresia in 7/12, progressive familial intrahepatic cholestasis in 3/12, and 2/12 with cytomegalo viral hepatitis (CMV). Most of them scored as Child–Pugh A (40.7%).

No patient of group 1 or group 2 had absolute adrenal insufficiency (Table 1). On the contrary children of group 1 showed higher basal cortisol level compared to children of group 2 as the mean value was 32.4 ± 14.8 vs 20.7 ± 3.4 μgm/dL ($P = 0.0$). Relative adrenal insufficiency was detected in 11 (45.8%) of the entire group of patients.

It was found that 8 (66.6%) patients of group 1 and 3 patients (25%) of group 2 had relative adrenal insufficiency (RAI) as the increment detected in cortisol level after stimulation was < 9 μgm/dL. This means a significantly higher inci-

Table 1 Clinical and laboratory data of the studied children.

	Group 1 (n = 12)	Group 2 (n = 12)	p
Age (months)	19.5 ± 10.0	23.9 ± 13.2	0.37
Gender M (%)/F (%)	5(41.7)/7(58.3)	5(41.7)/7(58.3)	1.0
Child–Pugh score: A/B/C (%)	1(8.3)/4(33.3)/7(58.3)	5(41.7)/4(33.3)/3(25.0)	0.05*
Ascites: present/absent (%)	8(66.6)/4(33.3)	4(33.3)/8(66.6)	0.1
Temp. (°C)	38.5 ± 0.5	37.2 ± 0.2	0.0*
CRP (mg/L)	43.0 ± 29.1	6.0 ± 0	0.01*
Leukocyte count ($\times 10^3$/mL)	17.0 ± 4.4	5.9 ± 0.9	0.0*
Neutrophils (%)	66.8 ± 8.2	40.3 ± 7.9	0.0*
Platelet count ($\times 10^3$/mL)	242.7 ± 145.3	201.3 ± 49.4	0.84
ALT (IU/L)	156.2 ± 117.1	101.3 ± 41.9	0.14
AST (IU/L)	186.8 ± 127.9	126.7 ± 74.4	0.22
Total bilirubin (mg/dL)	14.8 ± 8.7	7.7 ± 6.3	0.02*
Albumin (gm/dL)	2.4 ± 0.45	3.3 ± 0.7	0.004*
INR	1.6 ± 0.6	1.2 ± 0.1	0.03*
Creatinine (mg/dL)	0.5 ± 0.2	0.4 ± 0.9	0.28
Na (mEq/L)	130.9 ± 3.5	132.1 ± 4.3	0.48
K (mEq/L)	3.6 ± 0.5	3.8 ± 0.4	0.37
Basal S cortisol level (μg/dL)	32.4 ± 14.8	20.7 ± 3.4	0.0*
Peak 30 m after stimulation	39.5 ± 11.4	33 ± 6.8	0.03*

INR: international normalized ratio.
Na: sodium.
K: potassium.
S: serum.
ALT: alanin aminotransferase.
AST: aspartate aminotransferase.
CRP: C reactive protein.
* Significant.

dence of RAI in group 1 compared to group 2 (P = 0.05) (Fig. 1).

Most patients with RAI (72.7%) were categorized as Child–Pugh C liver cirrhosis indicating the relation between the degree of liver cirrhosis and the occurrence of RAI. The presence of ascites, high temperature, high CRP, neutrophilia, high ALT, AST, high total bilirubin, prolonged INR and lower albumin were all factors associated with the occurrence of RAI (Table 2).

Survival rate in patients with normal adrenal function (92%) was significantly better than in patients with RAI (27%) (P = 0.02) (Fig. 2). Four patients of the group with sepsis died during their hospital admission for sepsis and 3 shortly after.

4. Discussion

Patients with cirrhosis are susceptible to bacterial infection, which can result in circulatory dysfunction, renal failure, hepatic encephalopathy, and a decreased survival rate. Severe sepsis is frequently associated with adrenal insufficiency, which may lead to hemodynamic instability and a poor prognosis [13]. Recently, adrenal insufficiency has been demonstrated in patients with severe liver disease such as acute liver failure (ALF), acute on top of chronic liver failure (ACLF), recent liver transplantation and cirrhosis irrespective of the presence of sepsis. Nevertheless survival benefit with administration of hydrocortisone has only been demonstrated in patients with cirrhosis and septic shock [14].

Although no cases of absolute adrenal insufficiency have been detected among patients included in this study however, yet there was a high incidence of relative adrenal insufficiency (RAI) among patients with liver cirrhosis and sepsis as it was detected in 66.6% compared to 25% in the group of cirrhosis without sepsis. The overall reported incidence of adrenal insufficiency among patients with liver disease by Marik et al. [7] was 72%. The prevalence of adrenal insufficiency varied between their groups, being seen in 66% of ACLF patients, 33% of ALF patients and 61% of patients who had undergone

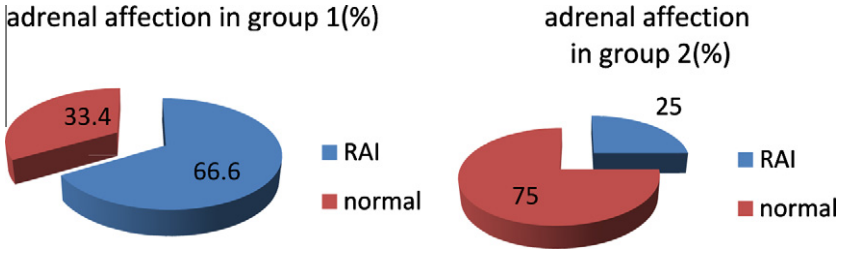

Figure 1 Adrenal affection in the studied groups.

Table 2 Comparison between patients with relative adrenal insufficiency (RAI) and patients without.

	Patients with RAI (n = 11)	Normal adrenal function (n = 13)	p
Age(months)	21.37 ± 12.3	22.07 ± 11.7	0.68
Gender: M (%)/F (%)	6(54.5)/5(45.5)	4(30.8)/9(69.2)	0.4
Child–Pugh score: A/B/C (%)	0(0)/3(27.3)/8(72.7)	6(46.2)/5(38.5)/2(15.4)	0.007*
Ascites: present/absent (%)	8(72.7)/3(27.3)	4(30.8)/9(69.2)	0.05*
Temp. (°C)	38.5 ± 0.7	37.5 ± 0.2	0.01*
CRP (mgl/L)	37.6 ± 33.4	13.3 ± 6.0	0.02*
Leukocyte count ($\times 10^3$/mL)	13.8 ± 6.1	9.4 ± 6.2	0.08
Neutrophils (%)	60.9 ± 14.7	47.3 ± 14.0	0.03*
Platelet count ($\times 10^3$/mL)	238.0 ± 147.5	208.5 ± 63.6	0.72
ALT (IU/L)	167.0 ± 107.3	96.3 ± 60.1	0.04*
AST (IU/L)	210.6 ± 119.2	111.1 ± 71.6	0.016*
Total bilirubin (mg/dL)	16.3 ± 8.0	7.1 ± 5.9	0.004*
Albumin (gm/dL)	2.4 ± 0.53	3.2 ± 0.7	0.01*
INR	1.6 ± 0.5	1.16 ± 0.13	0.002*
Creatinine (mg/dL)	0.5 ± 0.26	0.4 ± 0.18	0.37
Na (mEq/L)	130.3 ± 3.5	132.4 ± 4.1	0.22
K (mEq/L)	3.6 ± 0.4	3.9 ± 0.5	0.23
Survival rate	27%	92%	0.002*

* Significant.

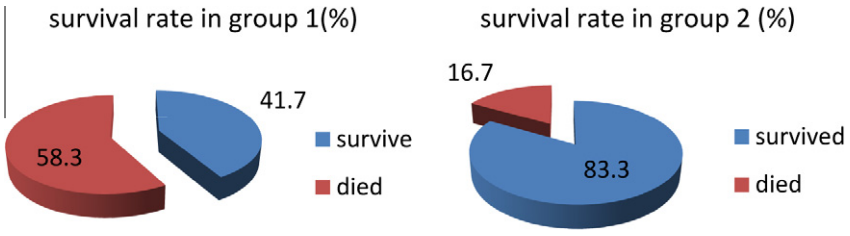

Figure 2 Survival rate in the studied groups.

liver transplantation in the past. Interestingly, of the patients recently undergoing liver transplantation with a steroid free regimen, the incidence of adrenal insufficiency was 92%. Harry et al. [15] evaluated 45 patients with acute hepatic dysfunction. The authors found subnormal short synacthen test and interpreted their findings as evidence that subnormal adrenal responses in liver dysfunction were related to the severity of the liver and multiple organ failure and independent of the presence of sepsis. However in the current study the adrenal insufficiency was related to the severity of liver disease and the presence of sepsis.

Hauser et al. [16], evaluated 22 children with end stage liver disease and found contrary to the present study that all patients had low baseline cortisol levels and ten also had an abnormal cosyntropin stimulation test. Mohamed et al. [17], in their study found that adrenocortical insufficiency was commonly present in patients with cirrhosis especially in patients complicated with hepatorenal syndrome. However in the current study no difference could be detected between the two groups regarding renal function.

It was evident in this study that relative adrenal insufficiency was related to the degree of liver cirrhosis being more common in Child C liver cirrhosis; however Marik et al. [7], found no differences in either the severity of the liver disease or the severity of the critical illness between patients with or without adrenal insufficiency, also Hauser et al. [16], concluded that the severity of adrenal insufficiency did not correlate with the degree of hepatic decompensation, clinical characteristics, including serum electrolytes and vasopressor requirements.

The issue of adrenal insufficiency has been explored in patients with chronic liver disease complicated by sepsis. In the study of Tsai et al. [13], 51% of their patients fulfilled the criteria for adrenal insufficiency, the degree of adrenal dysfunction correlated with disease severity as measured by Child–Pugh and the mortality rate increased in the adrenal insufficiency group. Also, in the present study the mortality rate was significantly high in the group with RAI. In the study of Fernandez et al. [18], the authors found RAI in 18/25 (68%) and this group of patients was treated with hydrocortisone. In the treated group of patients there was quicker resolution of shock and an apparent survival benefit compared to historical controls that had not undergone adrenal function testing. The survival rate in this study was poor in group 1 compared to group 2 (41.7% vs 88.3%), also in the study of Hauser et al. [16], 55% of their patients died in the hospital, and reported that hydrocortisone therapy permitted rapid weaning of vasopressor therapy but did not affect survival.

In a systematic review of literature O'Beirne et al. [19], concluded that patients with liver failure and especially those with sepsis have a high incidence of RAI and that the degree of adrenal dysfunction is correlated with the severity of the liver disease. This agrees with the findings in the present study. They also concluded that although the existing evidence is limited, the finding that RAI can be observed in acute liver failure patients with no apparent evidence of sepsis or in patients imme-

diately post liver transplantation suggests that RAI could be a feature of liver disease per se.

Whether RAI in liver disease is an entity specific to liver failure or occurs by the same mechanism as in sepsis is currently unknown and represents an exciting area for clinical research. There are scant data on the prevalence of adrenal dysfunction in cirrhosis and most importantly, the effect of corticosteroid therapy on mortality in patients with liver disease and RAI has never been examined in controlled studies [19].

Some authors suggested that low levels of HDL cholesterol may be responsible for the observed defects in adrenal function in liver disease [20]. Other authors demonstrated that patients with acute and chronic liver disease have increased levels of circulating endotoxin (lipopolysaccharide) and proinflammatory mediators such as tumor necrosis factor which cause reductions in CRH and ACTH release and therefore low levels of cortisol [21,22].

Other authors suggested that conditions such as liver failure where albumin and corticosteroid binding globulin (CBG) levels are reduced, total cortisol levels may be low whereas free cortisol levels may be normal or even increased as in serum, as 70% of circulating cortisol exists bound to (CBG), 20% is bound to albumin and 10% exists as biologically active free cortisol [23]. This led Galbois et al. [24] to conclude that using serum total cortisol assays overstate adrenal insufficiency prevalence among cirrhotic patients, mainly because of inaccurate concentrations related to hypoalbuminemia. Salivary cortisol assays should be preferably used in these patients. Montagnese et al. [25] assessed the 24-h rhythm of cortisol in patients with cirrhosis using plasma free cortisol assays, avoiding the bias of the reduced cortisol transport proteins. They report that patients with Child–Pugh B/C cirrhosis have significantly lower plasma free cortisol concentrations and that their rhythms onset and offset are (not significantly) delayed compared to patients with Child–Pugh A cirrhosis.

There are many arguments about the best method to assess adrenal function in patients with liver cirrhosis. Also there is continued controversy about the best diagnostic test for RAI, because of the limitations of the current case definitions. Only a few studies examined the effect of hydrocortisone therapy in patients with liver disease and showed improvement in hemodynamic abnormalities. However, the effect on survival was not consistent in these studies [26].

It was concluded from this study that a high incidence of relative adrenal insufficiency was found in children with liver cirrhosis. It was more common in the presence of sepsis, related to the degree of liver cirrhosis and carried a bad prognosis but further research in this area is needed to identify the best diagnostic and therapeutic approach to this important entity.

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