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Case Report

Adverse Effects of Ramadan Fasting in a Girl with Salt-Losing Congenital Adrenal Hyperplasia

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Abstract

Introduction: Congenital Adrenal Hyperplasia (CAH) is the most common cause of adrenal insufficiency in pediatrics. Chronic glucocorticoid replacement is the mainstay of treatment in the classic forms of CAH and mineralocorticoids replacement therapy is mandatory in salt-wasting form. Fasting is a mild stressor, which can expose to dehydration, hypotension, hypoglycemia and acute adrenal crisis in patients with adrenal insufficiency.

Case: We report the case of an adolescent affected by classic form with salt-losing CAH, who observed Ramadan for 30 days, without individualized therapeutic management plan. After Ramadan, a dramatic increase of ACTH level (1081 pg/ml), reduced cortisolemia, tendency to hypotension and weight loss was recorded. She experienced insomnia, intense thirst, asthenia and headache. The symptoms disappeared restarting the previous therapy schedule and increasing the total hydrocortisone daily dose with progressive restoring of hormonal control.

Conclusion: Our case confirm that patients with CAH are vulnerable, especially during fasting in Ramadan, with a higher risk of acute adrenal crisis. CAH patients should not be encouraged to fast, but if they do so, they will need individualized therapeutic plan and careful monitoring.

Keywords: Congenital adrenal hyperplasia; Ramadan; Fasting; Acute adrenal crisis; Personalized treatment

Established Facts and Novel Insights

Established Facts

- Congenital Adrenal Hyperplasia (CAH) is the most common cause of adrenal insufficiency in pediatrics
- Chronic glucocorticoid replacement is the mainstay of treatment in the classic forms of CAH. Mineralocorticoid replacement is also necessary in salt-wasting form.
- Fasting is a mild stressor which can expose to dehydration, hypotension, hypoglycemia and acute adrenal crisis patients with adrenal insufficiency.

Novel Insights

- During fasting in Ramadan, CAH patients are vulnerable, with a higher risk of acute adrenal crisis.
- The disruption of feeding and sleep schedules, in lack of an adequate adaptation in therapeutic management, leads to severe metabolic impairments in CAH
- CAH patients should not be encouraged to fast, but if they do so, they will need individualized therapeutic plan and careful monitoring to prevent adrenal acute crisis

Introduction

Congenital adrenal hyperplasia is the most common cause of adrenal insufficiency in pediatrics [1]. CAH comprises a family of autosomal recessive disorders that impairs adrenal steroidogenesis; the main form is due to 21-hydroxylase deficiency associated with mutations in the 21-hydroxylase gene (6p21). In the case of 21-OHD, the phenotypic spectrum ranges from virilization associated to salt-losing, to simple virilizing forms, to mild forms. The "classic form" includes salt-losing and simple virilizing forms. The mild form is also known as "late-onset or non-classic form" [1]. However, this classification system is somewhat artificial because disease severity due to a continuum based on residual enzyme activity [2]. Chronic glucocorticoid replacement is the mainstay of treatment in the classic forms of CAH. Mineralocorticoid replacement is also necessary in salt-wasting form. Patients in glucocorticoid treatment must double or triple hydrocortisone dose during intercurrent illness (fever, gastrointestinal illness), stressful life events, surgery, or trauma in order to prevent adrenal crisis [3].

Fasting is usually considered as a mild stressor. It can expose to dehydration, hypotension, hypoglycemia and acute adrenal crisis patients with adrenal insufficiency. Ramadan fasting is the fourth pillar of Islam. During this holy month, Muslims must abstain from drinking, eating and even taking oral medications, from sunrise to sunset. This practice is request to all the Muslims, beginning from adolescence, excluding pregnant women and ill subjects in which Ramadan can be dangerous [4]. Nevertheless, some people with chronic conditions still want to adhere fasting during Ramadan. Here we report the case of an adolescent affected by classic form with salt-losing CAH, who observed Ramadan for 30 days, without individualized therapeutic management plan.

Case Report

Patient is a 13 years old girl, third child of non-consanguineous parents, born at the end of a normal course pregnancy, by eutocic birth. Increased 17-OHP level (252 nmol/L) was found at Guthrie neonatal screening and confirmed by a second test (440 nmol/L). Classical CAH form with salt losing was diagnosed and replacement

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Table 1: Hormonal panel (8am), blood pressure, body weight and therapy of our patient before, during and after Ramadan.

	Before Ramadan	During Ramadan	3 Days after Ramadan	1 Month after Ramadan	8 Month after Ramadan
ACTH (pg/ml)	236	na	1081	875	16.3
17-OH P (ng/ml)	3.7	na	2.4	na	0.7
Cortisol (mcg/dl)	20.6	na	5	13.2	11.6
Blood pressure (mmHg)	125/80	na	90/60	120/80	110/60
Weight (Kg)	62	na	54	56	59
Hydrocortisone	8am: 10 mg; 1pm: 10 mg; 8pm: 5 mg	4am: 10 mg; 9pm: 10 mg; midnight: 5 mg	8 am: 10 mg; 1pm: 10 mg; 8pm: 10 mg	8 am: 10 mg; 1pm: 10 mg; 8pm: 10 mg	8am: 10 mg; 1pm: 10 mg; 8pm: 10 mg
Fludrocortisone	1pm: 0.1 mg	9pm: 0.1 mg	1pm: 0.1 mg	1pm: 0.1 mg	1pm: 0.1 mg

na=not available.

therapy with hydrocortisone, acetate fludrocortisone and NaCl oral supplementation was therefore started. During infancy and childhood, there were no remarkable events in her medical history except for episodes of febrile convulsions; secondary enuresis at the age of 6 was treated with oxybutynin for 6 months. Growth and neuropsycomotory development were normal. Menarche occurs at 12 years. During the follow-up (10 years), therapeutic adjustment in medications were related to weight gain and stress periods (fever). Despite the adherence of the therapy was not always optimal, major complications never occurred. The data at the last check-up visit [4] months before Ramadan beginning) was reported in (Table 1). On May 5th 2019, without consulting our Clinic or agreeing on therapeutic plans, the girl begins Ramadan, which she completes on June 3rd 2019 (30 total days). During Ramadan, the girl observed fasting from sunrise to sunset, having dinner at 9pm, a snack at midnight and an abundant breakfast at 4am. Consequently, the patient modified therapy schedule as reported in (Table 1). At the periodic endocrinological evaluation, which almost coincided with the end of Ramadan (June 6th 2019), we found dramatic increase of ACTH level, reduced cortisolemia, tendency to hypotension and important weight loss (-12.5% of body weight), (Table 1).

From the anamnestic collection, it emerged that during the fasting period the girl presented some difficulty falling asleep in the first days of Ramadan. She complained intense thirst and strong predilection for salty foods, mainly due to the fast and to the saline loss, compensated only during the night. She also reported onset of asthenia and episodes of daytime headache. During this control visit, we prescribed restoring of previous therapy schedule and increasing the total hydrocortisone daily dose to 30 mg. One month later this therapeutic change, the ACTH level was diminished, still indicative of poor control of the CAH, but the symptoms had disappeared and body weight increases of 2 kg. Four months later the end of Ramadan, ACTH hematic level further reduced and the cortisolemia was within normal ranges. Progressive restoring of hormonal control was reached, (Table 1). Finally, the patient and the family were discussed on the seriousness of the decision taken, and on the risks that the girl could have faced.

Discussion

Fasting during Ramadan is a stressful period, in which food and fluid ingestion are restricted from sunrise to sunset for a complete month, each year. As in our patient, during Ramadan, the disruption of feeding and sleep schedules in lack of an adequate adaptation in therapeutic management, influences the stress system response and leads to the disruption of cortisol circadian pattern, with lower levels in the morning and higher in the evening. The deregulation of the circadian cortisol rhythm, which acts as regulator between central and peripheral clocks in different tissues, can have metabolic adverse effects. In patients with adrenal insufficiency, particularly in subjects with Classic CAH, Ramadan fasting expose to risk of hypoglycemia, dehydration and this practice could be fatal [5]. The fatigue and asthenia, as noted in this case, can occur as symptoms of the hypoglycemic events. The pathogenic mechanism underlying hypoglycemia is accounted to low levels of cortisolemia, reduction of hepatic gluconeogenesis and increased sensitivity to insulin, due to relationship between the cortisol rhythm and the insulin resistance rhythm [5]. Fasting shifts from carbohydrates to fatty acids metabolism, using ketones as major cellular fuel source for body. In lack of exogenous glucose, counterregulatory hormones, such as glucagon, epinephrine, cortisol and growth hormone, stimulate hepatic glycogenolysis and gluconeogenesis to maintain glycemic homeostasis. A prevalent use of fatty acids from adipose tissue may also induced body weight loss. Although this reduction may seems beneficial, an exacerbation of this mechanism could lead to an acute adrenal crisis [5]. Changes in metabolic status may also induce sleep alteration. In our case sleeplessness could be related to higher levels of cortisol in the evening, due to assumption of two doses of hydrocortisone close to bedtime, when maximal glucocorticoid sensitivity of peripheral tissues is reported [4,7]. The observed metabolic impairments during Ramadan practice highlight the need of an individualized therapeutic management plan, with structured education and intensification of self-control. As reported [6], during Ramadan in CAH patients, longer acting glucocorticoids might replace or be combined with hydrocortisone in order to guarantee an appropriate cortisol daily curve. Furthermore, they might adequate their diet habits (avoiding sugars, processed starches, caffeine and other stimulant drugs, supplementing salt and drinking non-sugar-laden liquids) and physical activity (increasing resting in fasting and hotter hours). Education of these patients and caregivers is mandatory to recognize warning symptoms of adrenal insufficiency, such as asthenia, nausea and/or vomiting [6].

In conclusion, our case confirm that patients with CAH are vulnerable, especially during fasting in Ramadan, with a higher risk of acute adrenal crisis. CAH patients should not be encouraged to fast, but if they do so, they will need individualized therapeutic plan and careful monitoring.

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