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Two Neonatal 21-Hydroxylase Deficiency Cases without Hyperpigmentation

Ahmet Ozdemir[1], Selim Kurtoglu[1,2], Ulku Gul[2], Nihal Hatipoglu[2] and Tamer Gunes[1]*

[1]Department of Pediatrics, Division of Neonatology, Erciyes University, Turkey

[2]Department of Pediatrics, Division of Pediatric Endocrinology, Erciyes University, Turkey

Abstract

The majority of cases of salt-losing congenital adrenal hyperplasia present with 21-hydroxylase deficiency in the newborn period. In females it is recognized by the uncertainty of the external genitalia and in males by macro genitalia. The presence of hyperpigmentation is an important finding of adrenocorticotropic hormone along with melanocyte stimulating hormone, especially on the nipples and genitals in babies. However, some patients may not have hyperpigmentation. This paper emphasizes that patients with 21-hydroxylase deficiency may not always have hyperpigmentation and that surrenal ultrasonography is important in the diagnostic studies.

Keywords: Newborn; White Addison; 21-Hydoxylase deficiency

Introduction

Congenital Adrenal Hyperplasia (CAH) is a disease series which presents with enlargement of the adrenal glands with ACTH increase due to the deficiency of enzymes playing a role in cortisol synthesis [1,2]. The diseases include StAR, 3-beta–hydroxysteroid dehydrogenase deficiency (3β-OHSD), 21-hydroxylase and 11-hydroxylase deficiency, respectively in order, but the most common form is 21-hydroxylase deficiency. It is divided into two groups as classic or non-classic type [1-3]. Classic forms are examined under two groups, the type causing salt wasting and the common virilizing type. Most of the forms causing salt wasting in newborns are 21-hydroxylase deficiency cases. In female newborns, it can be observed as cases with a masculine external appearance with clitoromegaly, ambiguous genitalia or bilateral cryptorchidism or it may cause findings such as macrogenitalia in boys, pigmentation in the nipples-genital area or general hyperpigmentation in both genders [1-3]. However, pigmentation may not develop in every case. These cases are called "non-pigmented CAH" or "white Addison" [4,5]. The clinical significance of the topic was emphasized in this paper by presenting two cases who are hospitalized with salt wasting crisis presentation in which pigmentation was not observed.

Case Presentation

Case 1

It was learned that the 23 day old baby referred to our hospital with complaints of discomfort and inability to gain weight had been born full-term with a birth weight of 3260 gr but had been unable to gain weight since about 10 days of age and she was restless. In the physical examination, her weight was measured as 3220 gr, height as 51 cm, head circumference as 35.5 cm and blood pressure as 93/56 mmHg. Her external genital structure had a masculine appearance, phallus was 2.3 cm, bilateral scrotal structure was empty and gonads were un-palpable. There was no pigmentation in the nipple and genital area in the patient. Suitable water-electrolyte treatment was started after diagnosis of dehydration and surrenal deficiency with laboratory findings. In the abdominal ultrasonography made on the day she was hospitalized, the uterus and ovary structures were found and surrenal glands were bigger than normal size and in cerebriform structure. With karyotype and hormonal results, virilized female and salt depleting 21-hydroxylase deficiency were diagnosed (Table 1). Treatment with hydrocortisone, mineralocorticoid and salt replacement was started. In the peripherical blood sample of the patient which was evaluated for genetic diagnosis, deletion was detected in the CYP21A2 gene of the patient in line with 21-hydroxylase and salt wasting type.

Case 2

It was learned that the male baby brought to the hospital with diarrhea and vomiting complaints

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Correspondence:
Ahmet Ozdemir, Department of Pediatrics, Division of Neonatology, Erciyes University School of Medicine, Talas Street, 38039, Kayseri, Turkey, Tel: 00903522076666; Fax: 00903524375825; E-mail: dr.ozdemir@yahoo.com

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Table 1: Clinical and laboratory findings of two cases*.

Parameter	Case 1	Case 2
Time of presenting (day)	23	20
Complaint	Crying, weight loss	Diarrhea
External genitalia	Virilized female	Macrogenitalia male
Serum sodium (mEq/L)	112	125
Serum potassium (mEq/L)	7.9	7.28
Plasma renin activity (ng/ml/s)	78.68	150.42
Serum aldosterone (pg/ml)	2147	135.72
Thrombocytosis (mm^3/kan)	763	894
Cortisol (µg/dl)	77.13	0.01
ACTH (pg/ml)	7560	420
17-OHP (ng/ml)	100	80
Total testosterone (ng/dl)	850	482
Adrenal gland ultrasonography (length and thickness)	Right 40 mm x 4 mm,	Right 27 x 4.5,
	left 35 mm x 5 mm	left 30 mm x 6 mm
	Cerebriform image	
Karyotype	46XX	46XY
Genetic study	CYP21A2 gene deletion	CYP21A2 gene deletion

*: Hormonal parameters were performed with radioimmunoassay (RIA) method.
ACTH: Adrenocorticotropic Hormone; 17 OHP: 17-Hydroxyprogesterone

on his postnatal 20th day had been born full-term with a birth weight of 3800 gr. Diarrhea-vomiting complaints had started on approximately the 13th day after birth and he was unable gain weight. His height was 53 cm, weight was 3650 gr, head circumference was 38 cm and average blood pressure was 55 mmHg in his physical examination. In the genital examination of the infant, who had a low fontanel and dry mouth, it was observed that the testicles were in the scrotum and the penis length was 4.5 cm (normal: 2.5 cm to 4.5 cm). There was no pigmentation in the nipple and genital area of the patient. Dehydration and surrenal deficiency were considered since thrombocytosis was also present in the patient in addition to hyponatremia and hyperpotassemia. In surrenal ultrasonography, it was observed that the surrenal glands were bigger than normal. The hormonal findings of the infant, who was started on dehydration and surrenal crisis treatment, were in line with salt wasting 21-hydroxylase deficiency (Table 1). Hydrocortisone, mineralocorticoid and salt replacement treatment was started and in the peripherical blood sample of the patient evaluated for genetic diagnosis, deletion was detected in the CYP21A2 gene of the patient in line with 21-hydroxylase and salt wasting type.

Discussion

Salt wasting 21-hydroxylase deficiency accounts for most of the surrenal crisis cases seen in the newborn period [1-3]. Clinical presentation of the cases is related to cortisol and mineralocorticoid deficiency. Also virilization in females and macrogenital structure in males occur due to increased androgen levels [1]. Another significant and stimulating physical examination finding in the diagnosis of the patients is hyperpigmentation which is more significant in the nipples, axillary and genital area [1]. Hyperpigmentation is related to increased melanocyte-stimulating hormone (MSH) level with increased ACTH. Serum and urine electrolytes, plasma renin activity, aldosterone, cortisol, 17-OHP, Dehydroepiandrosterone Sulfate (DHEA-S), androstenedione and total testosterone levels are studied in patients after physical examination. The definite diagnosis is made with the presence of mutations with genetic study. The presence of thrombocytosis in addition to hyponatremia and hyperpotasemia in cases with hyperpigmentation supports surrenal crisis [6,7]. Indeed, thrombocytosis was observed in both infants.

It is important to examine the surrenal gland and inner genital organs with ultrasonography in these cases. While surrenal ultrasonography adrenal gland dimensions in normal newborns are nearly 14.4 mm in length and 1.9 mm in width, these measurements are above 20 mm and 4 mm, respectively, if surrenal hyperplasia is present [8]. Another important finding is a cerebriform appearance in the surrenal glands [9]. The surrenal glands were large in both of our cases and cerebriform appearance was present in one of them. It should not be forgotten that renal pathologies may also cause pseudohypoaldosteronism in cases presenting with salt wasting crisis and renal ultrasonographic evaluation should also be done in addition to surrenal evaluation [10].

ACTH and melanocortin level increases in congenital adrenal hyperplasia cause pigmentation on the skin. Melanocytes are the population of intraepidermal dendritic cells occurring on the 50th day of intrauterine life and they produce melanin pigment [11]. Connecting to the ACTH and melanocortin melanocyte receptors, they cause an abnormal increase in melanin production. However, in some of the primary adrenal deficiency cases, it was observed that pigmentation did not form and the cases were named "white Addison" [12,13]. Some patients with a disorder affecting the hypothalamus and hypophysis may be pale as ACTH and MSH levels decrease [13]. However, although ACTH and MSH levels are high, a pigmentation loss due to a high degree of melanosome decomposition occurs in melanin-producing cells [4,5]. The reason for melanosome decomposition is not clearly known. Pigmentation loss in addition to very high ACTH was also observed in our cases.

Similarly, no pigmentation increase was observed in a case with

familial glucocorticoid deficiency demonstrating high ACTH-related hyperpigmentation. When the reason was examined, it was reported that pigmentation did not occur because there was a mutation in the ACTH receptor genes the melanocortin 1 receptor (MC1R) and melanocortin 2 receptor (MC2R) [14].

As a result, the presence of pigmentation in CAH diagnosis, which is the main reason for neonatal surrenal crisis that is life-threatening and which should be treated with early diagnosis, is an important finding. However pigmentation increase may not always take place, as in our case.

Conclusion

Even though there is no pigmentation increase in newborn cases with presentation of dehydration, hyponatremia, hyperpotassemia and thrombocytosis, we would like to emphasize the need to conduct urgent surrenal and renal ultrasonography in addition to hormonal evaluations for CAH diagnosis.

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