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Adrenomedullary Function in 21-Hydroxilase Deficiency. Is There an Association with adrenal Crises?

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Abstract

Background

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is characterized by impairment in normal steroid production. Patients with the most severe forms also have decreased adrenomedullary function. However, the clinical implications of epinephrine deficiency are not clear.

Objetive

Evaluate the adrenomedullary function in children with salt wasting congenital adrenal hyperplasia (SW CAH) and assess its relationship to the number of hospitalizations due to adrenal crises. We compare the clinical, analytical and genotypic characteristics and the therapeutic needs of patients with and without adrenomedullary disfunction.

Methods

We measured 24-hours urine catecholamine levels (epinephrine, norepinephrine and dopamine) and 21-hydroxilase genotype in 21 SW CAH.

Results

11 SW CAH had adrenomedullary disfunction characterized by undetectable urine epinephrine, and interestingly, had >8 adrenal crises during infanthood. Other 10 SW CAH had normal values of urine epinephrine and had less than 4 adrenal crises during infanthood. There were no significant differences in hydrocortisone (16.08 ± 3.4 mg/m2/day vs 16.98 ± 5.01 mg/m2/day) and 9fluorohydroxortisone (0.072 ± 0.06 mg/m^2/day vs 0,101 ± 0.12 mg/m^2 /day) doses, although the mean value of 17-OHP (0.04 ng/ml (0.1-1.3) vs 26.7 ng/ml (0.1-79)); ATCH (45pg/ml (30.9-122)vs 71 pg/ml (34-271)), aldosterone (50 pg/ml (50-50) vs 50 pg/ml (50-244)), and androstenedione (0 ng/ml (0-0,4) vs 2,6 ng/ml (0-5.3)) was lower in patients with undetectable urine epinephrine. 11 SW CAH with urinary epinephrine deficiency had most severe genotype.

Conclusion

SW CAH with undetectable epinephrine in urine had several crises during infanthood. The measurement of urine epinephrine is well correlated with the clinical severity of the disease and the expected activity of 21-hydroxilase.

Key words

Adrenal cortex; adrenal medulla; HPA axis; congenital adrenal hiperplasia; 21-hydroxylase deficiency.

Introduction

Congenital adrenal hyperplasia (CAH) defines a group of congenital diseases in which an error occurs in suprarenal steroidogenesis. The most common form of this condition is 21-hydroxylase deficiency (21-OHD). The synthesis of glucocorticoids, mineralocorticoids and androgens can be globally or partially affected, resulting in a heterogeneous group of clinical conditions [1-3].

Patients with the more severe forms of this disease not only present adrenal cortex dysfunction but also medullary dysfunction, with reduced catecholamine production [4]. This condition is due to the fact that the cortex and medulla are intimately related, ontogenically, anatomically and functionally, interacting and regulating their respective functions. This intimate relationship begins at the foetal stage. The chromaffin precursor cells migrate to the primordial adrenal gland in the sixth week of pregnancy and begin their differentiation to mature chromaffin cells under the influence of glucocorticoids. High concentrations of intraadrenal glucocorticoids are necessary for the induction of phenylethanolamine N-methyltransferase (PNMT), an enzyme that catalyses the passage of norepinephrine to epinephrine during the foetal stage, in childhood and in adulthood. Aldosterone also stimulates catecholamine synthesis, activating the enzyme that limits its synthesis (tyrosine hydroxylase). The adrenal androgens regulate the differentiation process of the chromaffin cells. Consequently, abnormalities in the adrenal cortex can affect the function of chromaffin cells and viceversa [4-9].

In our daily clinical practice, we have observed that some patients with the more severe forms of CAH due to 21-hydroxylase deficiency have numerous decompensations in response to a febrile illness or other stress situation, despite appropriate treatment with glucocorticoids and mineralocorticoids and good treatment adherence. The patients frequently visit hospital centres requiring fluid therapy and parenteral glucocorticoids for stabilisation despite having increased the dosage of glucocorticoids at home [10].

These patients could have adrenomedullary dysfunction, with impaired corticomedullary signalling, synchronisation and interaction, which would make them more susceptible to decompensations under conditions of stress or disease. The aim of our study was to study the adrenomedullary function in these patients and assess its relationship to the number of hospitalizations due to an adrenal crises. We compared the clinical, analytical and genotypic characteristics and the therapeutic needs of patients with and without adrenomedullary dysfunction.

Patients and Methods

We performed a cross-sectional descriptive study, which included 21 patients diagnosed salt-wasting CAH (6 female and 15 male patients, with a mean age 8.94 ± 6.74 years).

Laboratory tests were performed for the extraction of 17-hydroxyprogesterone, cortisol, aldosterone, androstenedione, plasma renin activity and adrenocorticotropic hormone between 8:00 am and 9:00 am after a 9-10 hour fast and before taking the morning medication and rested in a supine position for a minimum of 30 min before samples were collected.

To study the adrenomedullary function, we measured catecholamine levels in 24-h urine. The urine containers with stabiliser (6M HCl) were refrigerated (-2 – 6 °C) until taken to the laboratory. The method employed was high-performance liquid chromatography. The technique's sensitivity for detecting epinephrine, norepinephrine and dopamine was 2.2 μg/L, 2 μg/L and 6.5 μg/L, respectively, with a coefficient of variation of 4.8%, 1.1% and 4.1%, respectively. Due to the fact that a number of patients had "undetectable" catecholamine levels, we considered adrenomedullary dysfunction when the epinephrine, norepinephrine and dopamine levels in urine were ≤ -2.5 SD of the reference range for the patients' age or were outside the lower range of normality for adulthood. We considered that the patients with values > -2.5 SD or in the range for adulthood showed no adrenomedullary dysfunction [11].

The CYP21A2 genotyping was performed using Southern blot and polymerase chain reaction with allele-specific hybridisation using polymorphic microsatellite markers in the HLA region, classifying the results into 4 groups [14-17]: The Null Group (N=10) consisted of patients who were homozygous for mutations previously shown to confer no 21-hydroxylase activity (gene deletions, large gene conversions, Q318X, 8-bp deletion, 306InsT and R356W). Group A (N=11) were homozygous for the In2 mutation or compound heterozygous carrying an In2 mutation on one allele and a null mutation on the other allele (In2/In2 or In2/Null). Group B (N=0) included moderately milder mutations (I172N mutation homozygous or compound heterozygous with more severe mutations). Group C (N=0) included patients who were homozygous for P30L and Val281L or compound heterozygous with more severe mutations from other groups.

To identify and analyse the relevant decompensation crises, we defined adrenal crisis as a profound impairment of general health, with (A), at least two of the following clinical features: severe fatigue, nausea or vomiting, drowsiness, hypotension, hyponatremia (<132 mmol/L) or hyperkalaemia, hypoglycaemia; and (B), clinical deterioration precipitated by a glucocorticoid deficit state, or clinical improvement after the administration of glucocorticoids [12, 18]. The clinical and analytical information from these crises were obtained from the medical reports provided by the parents.

Statistical analysis was performed using the statistical programme SPSS, version 21.0 for Windows. Statistical significance was established for all analyses when p < 0.05.

Results

Adrenomedullary function

Eleven of the 21 patients had "undetectable" epinephrine values in urine or ≤ -2.5 SD for their age and sex. All children had norepinephrine and dopamine levels within normal limits. We compared the clinical and analytical data between the 2 groups and found that the mean adrenal androgen levels were lower in the patients with epinephrine deficiency, although the differences were statistically significant for cortisol, androstenedione and aldosterone (Table 1).

	Undetectable urinary epinephrine (N=11)	Detectable urinary epinephrine (N=10)	P value(stadistical significance p < 0.05)
Age, y*	6.14 ± 4.99	12.14 ± 7.24	0.038
zBMI*	-0.08 ± 1.15	1.0 ± 1.43	0.07
17-OHP**(N:0.1-1.5 ng/mL)	0.4 (0.1-1.3)	16.7 (0.1-79)	0.11
ACTH**(10-50 pg/mL)	45 (30.9-122)	71 (34-271)	0.5
Cortisol**(N: 5-25 μg/dL	0 (0-0)	2.08 (1.1-2.8)	0.002
Aldosterone**(N: 10-150 pg/mL)	50 (50-50)	50 (50-244)	0.008
Androstenedione** (N: 0.4-3.5 ng/mL)	0 (0-0.4)	2.6 (0-5.3)	0.01
Testosterone**(N: 0.1-0.8 ng/mL)	0.1 (0-0.2)	0.3 (0.08-2.13)	0.5
PRA ** (N: 0.15-2.4 ng/mL/h)	1.7 (0.3-2)	1.7 (0.8-3.1)	0.15
Hydrocortisone* (mg/m²/day)	16.08±3.4	16.98±5.01	0.6
9Fluorohydrocortisone* (mg/m²/day)	0.072±0.06	0.101±0.12	0.4

Table 1. Adrenomedullary function, clinical characteristics and biochemical findings in all 21 participants Abbreviations: 17-OHP, 17-hydroxyprogesterone; ACTH, adrenocorticotropic hormone; PRA, plasma renin activity; zBMI, body mass index z-score.
*Data are presented as means ± SD
**Data are presented as median with interquartile range (25th; 75th percentiles).

Relationship between adrenomedullary function and clinical decompensations

All patients with undetectable epinephrine levels in urine (N=11) had more than 8 decompensations. Three of the children with epinephrine in urine had less than 4 decompensations, while 7 children had no decompensation crises (p < 0.001).
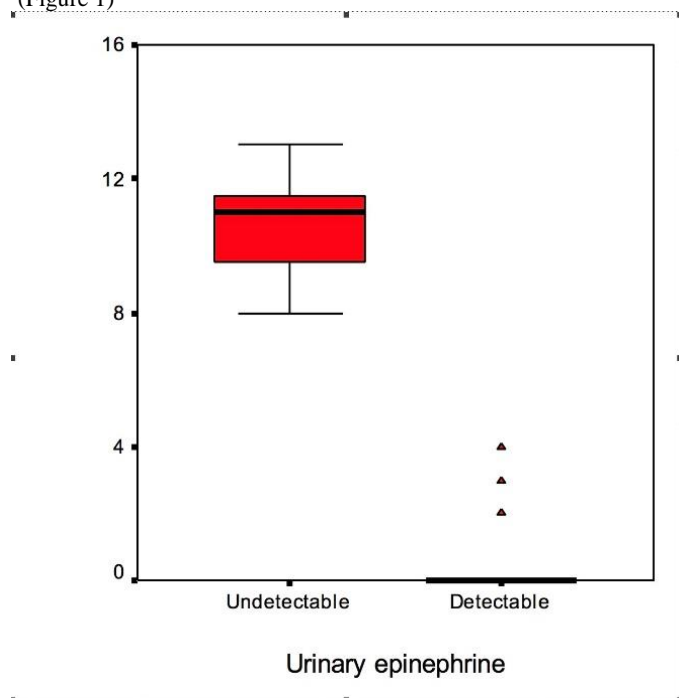 (Figure 1)

Figure 1. Number of adrenal crises and urinary epinephrine levels. All patients with undetectable epinephrine levels in urine had ≥ 8 decompensations while children with epinephrine in urine had ≤ 4 decompensations (p < 0.001)

The three children who had less than 4 decompensations presentedurine epinephrine values in the lower detection limit of our laboratory (2, 2 μgr/L).

These crises were recorded in less than 4 years, mainly in the first 2

years of life. All of these patients adequately complied with the glucocorticoid and mineralocorticoid treatment, and they were advised to increase the dose of glucocorticoids according to the intensity of the stess. The fact, 84% had increased the dosage of corticosteroids prior to arrival at a medical centre.

Table 2 shows the reasons for consultation and the parameters in the emergency department.

Table 2. Clinical and laboratory parameters in the emergency department.

Reason for consultation	%
Fever	86.50%
Vomiting	74.30%
Weakness	68.20%
Diarrhoea	10.90%
Cough	3.60%

SBP	DBP	HR	T (ºC)	Na (mmol/L)	K (mmol/L)	Glu (mg/dL)
106±11.46	68±8.8	108±20.4	38.01±1.3	135.1±3.99	3.9±0.55	85.2±15.8

Table 2. Clinical and laboratory parameters in the emergency department Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; Na, sodium; K, potassium; Glu, glucose; T, temperature. Data expressed as mean ± standard deviation.

Mutation analysis findings

The combination of allele-specific PCR and Southern blotting allowed the detection of the 46 alleles. The full spectrum of genotypes was shown in table 3. Gene deletions were present in 15 alleles (32.6%) and the most frequent point mutation was the intron2 splice site mutation (In2), wich was found in a total of 12 alleles (26%). Other mutations frequently detected included the Q318X in 6 alelles (13%) and V281L in 4 alelles (8, 6%). (Table 3)
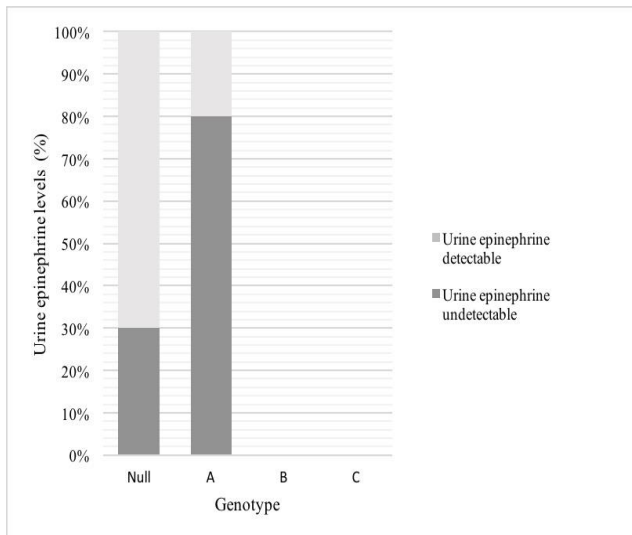
Table 3 Genotype.

Genotype	Number of participants	Total participants	Group
-Deletion/deletion	2	10	Null
-Deletion/306Isnt, 306Isnt+Val281L	2		
-R356W/Q318X, 306Isnt+V281L, Q318X+I172N, In2+8-pb deletion	4		
-Q318X/ Q318X, Q318X+R356W	2		
-In2/deletion	4	1	A
-In2/Q318X, 306Inst+V281L	2	1	
-In2/conversion	2		
-In2+V281L/Q318X, conversion	2		
-In2/In2	1		

Table 3: Genotype.

Relationship between adrenomedullary function and genotype

The patients with undetectable epinephrine levels in urine had mutations with null or minimal CYP21A2 activity: 3 had mutations that impeded the enzyme activity of 21-hydroxylase in both alleles (Null group), while 8 were compound heterozygous for intron 2 mutations (group A) (Figure 2).

Figure 2: Adrenomedullary function and genotype.
The patients with undetectable epinephrine urine levels had mutations that confer no 21-hydroxilase activity (Null group) or very low, but detectable, enzymatic activity *in vitro* (Group A). No patient had milder mutations (Group B or C).

Discussion

In our study, we observed that those patients with more decompensations (>8) despite appropriate treatment with glucocorticoids and mineralocorticoids had adrenomedullary hypofunction. Adrenomedullary dysfunction has been characterised by an epinephrine deficit in urine. These adrenal crises, when treated in emergency departments, are characterised by severe impairment of general health, with no associated tachycardia despite the fever, and ions and glucose in blood also frequently within normal limits. This fact, coupled with appropriate replacement with glucocorticoids and mineralocorticoids, could not prevent the adrenal crisis, despite 84% of the patients having already had their dosage of glucocorticoids increased before seeking treatment in the emergency department, a finding that suggests that epinephrine plays an important role in this decompensation situation.

To analyse the adrenomedullary function, we measured catecholamine levels in 24-h urine: epinephrine norepinephrine and dopamine. There were differences in the measurement of epinephrine in urine but not in norepinephrine or dopamine. Practically all circulating epinephrine is derived from the adrenal medulla. The epinephrine already released by the central nervous system cannot penetrate the blood-brain barrier. In contrast, norepinephrine comes from the synapses of the postganglionic sympathetic neurons and dopamine from its synthesis in the renal tubules. The main advantage of measuring in urine compared with blood is that the former is easy to access and can be performed at a minimum cost. The analysis is simple with low urine concentrations and is a well-established technique for detecting secretory tumours. The potential problems with this technique are the difficulty in collecting urine from young children, establishing reference intervals for this patient group and the inappropriateness of the technique for those with renal failure.

All patients with adrenomedullary dysfunction have undetectable cortisol levels in blood, which reflects an intense impairment of glucocorticoid synthesis. The probability that this is due to the treatment is low due to the half-life of hydrocortisone. Studies have observed that cortisol concentrations are undetectable 7 hours after the morning dose and 9 hours after the nighttime dose [19, 20]. In this study, the laboratory tests were performed in the morning at least 9-10 hours after the nighttime dose. This suggests that the analysed cortisol more likely reflects the endogenous production of glucocorticoids. However, the mean dose of hydrocortisone at the time of the study was similar in all the children with salt-wasting CAH (16.08 ± 3.4 mg/m²/day in patients with undetectable urinay epinephrine levels vs. 16.98 ± 5.01 mg/m²/day in patients with detectable urinay epinephrine levels), regardless of adrenomedullary dysfunction. The fact that adrenal androgens are more suppressed in children with numerous adrenal crises suggests that the children are being administered comparatively larger doses of glucocorticoids. These differences are probably due to the age at the time of the study, given that the patients with adrenal dysfunction are preschool and school aged, while the patients without adrenal dysfunction are in puberty. During puberty, a series of endocrine disorders occur that influence the pharmacokinetics of cortisol, resulting in inadequate suppression of the hypothalamic-pituitary-adrenal axis and suboptimal control despite appropriate treatment [21].

The epinephrine deficiency in urine correlates well with the most severe genotype (groups 1 and 2), which suggests that hypofunction severity is directly related to enzyme deficiency and consequently with cortex dysfunction. Twenty-seven percent of the patients with adrenomedullary dysfunction had mutations that confer no 21-hydroxilase activity (Null group), while 73% had intron 2 RNAm processing mutations in compound heterozygosity with another severe mutation (group A). In this study, intron2 mutation in compound heterozygosity with a null mutation has behaved clinical and functionally as if it were a Null group mutation. This has been attributed to the variable 21-hydroxylase activity conferred by the intron2, the variety of mutations often observed in patients who are compound heterozygotes, the possibility of additional not yet identified mutations, or the genetic variations in extraadrenal 21-hydroxylase activity [1, 12]

The medullar dysfunction observed in patients with 21-hydroxylase deficiency could be due to an impairment in the development of the formation of the medulla during embryogenesis, probably due to an intrauterine cortisol deficit, the unknown effects of CYP21A2, a deficit in intraadrenal steroids at the time of the study, a defect in PNMT expression or a combination of several factors. However, the fact that neither larger doses of hydrocortisone nor the doubling of the oral hydrocortisone dose during the adrenal crisis were sufficient to increase intraadrenal PNMT expression suggests a defect in the formation and/or maturation of the adrenal gland [22, 23 & 24].

Catecholamines influence practically all tissues. However, the clinical implications of epinephrine deficiency in humans have not been clarified, although the reduction in epinephrine could explain the greater susceptibility to developing hypoglycemia in children with CAH, cardiovascular instability under conditions of stress, such as infections and trauma and the poor tolerance to physical exercise [8, 25, and 26]. This is particularly important during the period of transition to extrauterine life, when the adrenal gland must adapt to the relatively hostile extrauterine environment after the disruption of the fetoplacental unit at birth. The increase in catecholamine levels during childbirth induces critical cardiovascular adaptations: increased blood pressure and cardiac ionotropic effects, increased glucagon secretion, and reduced insulin secretion, increased thermogenesis in the brown adipose tissue and the release of surfactants [27]. In fact, some SW CAH patients have been hospitalized in the first 3-5 days of life due to unconfirmed clinical sepsis. Cortisol deficiency, aggravated by catecholamine deficiency, probably contributes to this poor extrauterine adaptation.

In conclusion, the measurement of epinephrine in urine is well correlated with the clinical severity of the disease, with the expected phenotype and activity of the 21-hydroxylase according to the molecular genetic analysis. Conventional treatment with glucocorticoids and mineralocorticoids does not prevent decompensation crises, and new therapeutic strategies need to be tested [36].

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