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CLINICAL CASE SEMINAR

A Particular Phenotype in a Girl with Aldosterone Synthase Deficiency

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Aldosterone synthase deficiency (ASD) usually presents in infancy as a life-threatening electrolyte imbalance. A 4-wk-old child of unrelated parents was examined for failure to thrive and salt-wasting. Notable laboratory findings were hyperkalemia, high plasma renin, and low-normal aldosterone levels. Urinary metabolite ratios of corticosterone/18-hydroxycorticosterone and 18-hydroxycorticosterone/aldosterone were intermediate between ASD type I and type II. Sequence analysis of *CYP11B2*, the gene encoding aldosterone synthase (P450c11AS), revealed that the patient was a compound heterozygote carrying a previously described mutation located in exon 4 causing a premature stop codon (E255X) and a further, novel mutation in exon 5 that also causes a premature stop codon (Q272X). The patient's unaffected father was a heterozygous carrier of the E255X mutation, whereas the unaffected mother was a heterozygous carrier of the Q272X mutation. Therefore, the patient's *CYP11B2* encodes two truncated forms of aldosterone synthase predicted to be inactive because they lack critical active site residues as well as the heme-binding site. This case of ASD is of particular interest because despite the apparent lack of aldosterone synthase activity, the patient displays low-normal aldosterone levels, thus raising the question of its source. (*J Clin Endocrinol Metab* 89: 3168–3172, 2004)

ALDOSTERONE IS THE principal mineralocorticoid hormone in humans and is synthesized by aldosterone synthase (CYP11B2) in the adrenal zona glomerulosa. Conversion of deoxycorticosterone (DOC) to aldosterone requires hydroxylation at position 11β to form corticosterone (B), hydroxylation at position 18 to form 18-hydroxycorticosterone (18OHB), and finally oxidation at position 18. All three reactions require the same enzyme, CYP11B2 (1). Aldosterone synthase deficiency (ASD) usually presents in infancy as a life-threatening electrolyte imbalance. Affected children typically display failure to thrive, vomiting, and severe dehydration; the biochemical features are hyperkalemia, hyponatremia, and metabolic acidosis with elevated plasma renin activity and low or undetectable aldosterone (2–4). Patients with aldosterone synthase deficiency type 1 (ASD1), display undetectable aldosterone levels, increased levels of 18-hydroxy-11-deoxycorticosterone (18OHDOC), reduced levels of 18OHB, and an increased B/18OHB ratio. ASD-1 is caused by mutations in CYP11B2 that result in the expression of loss of function enzymes; for example, *in vitro* expression in COS cells of aldosterone synthase mutants carrying L461P or R384P substitutions or a truncated enzyme derived from five nucleotide deletions in exon 1 produce forms of aldosterone synthase that lack all three enzyme activities (5–7). In contrast, ASD2 is characterized by low aldosterone levels, increased 18OHB and 18OHDOC levels, and an increased 18OHB/aldosterone ratio. This form of ASD is caused by mutations that impair both 18-hydroxylase and oxidase activities, whereas the 11β-hydroxylase activity is retained (2–4, 8–10). The genotype/phenotype correlation in this disease is not always straightforward; for example, patients with clinical ASD1 have been described who exhibit the genetic defect typical of ASD2 (11) as well as patients with clinical ASD1 associated with a normal CYP11B2 gene (12).

In this study we report an unusual case of a girl who is a compound heterozygote for nonsense mutations that encode a truncated protein, but displays biochemical features intermediate between those of ASD1 and ASD2.

Abbreviations: ASD, Aldosterone synthase deficiency; B, corticosterone; DOC, deoxycorticosterone; HML, human mononuclear leukocyte; 18OHB, 18-hydroxycorticosterone.

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Subjects and Methods

Informed consent was obtained from the parents both on their behalf and on behalf of their child for the biochemical and genetic studies described herein.

Clinical details

An apparently normal female infant was born at 39 wk gestation. Birth weight was 3100 g, and length was 50 cm. The parents are Italian Caucasian and nonconsanguineous. At 4 wk of age she was admitted to hospital for vomiting and failure to thrive that persisted despite assumption of 110 cal/kg·d (460.2 J/kg·d). She displayed hyponatremia (serum sodium, 131 mmol/liter; normal range, 136–145 mmol/liter),

hyperkalemia (serum potassium, 6.5 mmol/liter; normal range, 3.5–5.0 mmol/liter), and metabolic acidosis. A 24-h urinary sodium level was low (3 mmol/24 h; normal, 60–200 mmol/24 h).

There were no signs of salt-wasting nephropathy or enteropathy, urinary trait infection, or obstruction. The diagnosis of pyloric stenosis was ruled out by ultrasonography of the abdomen. Whole blood was taken to obtain a buffy coat for the receptor binding studies and genomic DNA extraction. Morning plasma and 24-h urine were taken for hormonal assays. Recumbent aldosterone was between 2.9 and 10.9 ng/dl [80.4–302.4 pmol/liter; normal range for age, 5–60 ng/dl (138.7–1,664.4 pmol/liter)], and active renin was between 8,000 and 38,240 ng/liter [4,800–23,000 mU/liter; normal range, 5–24 ng/liter (3–14.5 mU/liter)] after multiple determinations. Plasma and urinary cortisol and plasma 17-hydroxyprogesterone levels were normal, indicating the absence of 21-hydroxylase deficiency or other disorders affecting the entire gland, for example, Addison's disease and adrenal hypoplasia. NaCl (16 mEq/d) and $NaHCO_3$ (12 mEq/d) were administered until fludrocortisone therapy was initiated at 9 wk of age. Seven days of sodium supplementation were necessary to correct the hyponatremia and the metabolic acidosis. The patient underwent therapy with fludrocortisone (0.1 mg/d) and sodium bicarbonate supplementation, with regression of the symptoms and normalization of the weight increase.

Hormonal assays

Urinary hormones were measured by gas chromatography-mass spectrometry as described previously (13). Plasma active renin and plasma aldosterone were measured by RIA [kit purchased from CIS Biointernational (Gif-sur-Yvette, France) and Diasorin (Vercelli, Italy)]. Plasma 18OHB and B were measured as described previously (14, 15).

Aldosterone receptor binding study

Human mononuclear leukocytes (HML) were separated from whole blood as described previously (16). Briefly, HML were isolated on Percoll gradients, and an aliquot was incubated with increasing amounts of [^{3}H]aldosterone alone or with an excess of cold competitor. An excess of a pure glucocorticoid (RU26988; Roussel-UCLAF, Romainville, France) was added to prevent binding of aldosterone to glucocorticoid receptors. After incubation for 1 h at 37 C, cells were washed, their radioactivity was measured, and results were expressed by Scatchard analysis.

Genetic studies

Blood samples were obtained from the patient and both parents, and genomic DNA was extracted as described previously (17). All nine exons of *CYP11B2* of the patient were specifically amplified by PCR in two fragments (exons 1–5 and exons 6–9) as previously described (18). The PCR products were purified using a High Pure PCR product purification kit (Roche, Indianapolis, IN) and an aliquot (1:20) was used for direct sequencing on an ABI PRISM 310 DNA sequencer (PE Applied Biosystems, Foster City, CA). For confirmation of genotypes by restriction enzyme digests, fragments of exon 4 or exon 5 were amplified using the PCR product of exons 1–5 as template. Amplification of fragments of exon 4 (forward primer, 5′-ACCGTCCAGCTCATGTTCA-3′; reverse primer, 5′-GCCTCACCGTACTGGAAGAT-3′) or exon 5 (forward primer, 5′-CACCAAGATCTGAGGGCTGT-3′; reverse primer, 5′-CCACGATGCCTGTGTAGTGT-3′) was performed in 20 μl containing 10 pmol of each primer, 15 mmol/liter Tris-HCl (pH 8.0), 50 mmol/liter KCl, 1.5 mmol/liter $MgCl_2$, 250 μmol/liter of each deoxydinucleotide triphosphate, and 1 U AmpliTaq Gold *Taq* polymerase. The cycling conditions were 95 C for 5 min; 35 cycles of 95 C for 20 sec, 55 C for 20 sec, and 72 C for 20 sec; and 10 min at 72 C. Aliquots (10 μl) of the exon 4 and exon 5 PCR fragments were incubated with either 3 U *Sdu*I or 3 U *Xba*I (MBI Fermentas, Inc., Hanover, MD) for 2 h at 37 C. The digested products were resolved on 4% Metaphor agarose gels (BioWhittaker Molecular Applications, Rockland, ME).

Results

Clinical data

Urinary steroid measurements revealed normal levels of tetrahydrodeoxycorticosterone [6.47 μg/24 h (19.4 nmol/24 h); normal range, 0.2–17 μg/24 h (0.6–50.9 nmol/24 h)], tetrahydrocorticosterone [10.1 μg/24 h (28.9 nmol/24 h); normal, 2–13 μg/24 h (5.7–37.1 nmol/24 h)], terahydro-18-hydroxy-11-dehydrocorticosterone [18.2 μg/24 h (50 nmol/24 h); normal, 3–25 μg/24 h (8.2–68.7 nmol/24 h)], and tetrahydroaldosterone [4.6 μg/24 h (12.6 nmol/24 h); normal, 0.2–20 μg/24 h (0.5–55 nmol/24 h)]; a mild increase in tetrahydro-5α-corticosterone [137 μg/24 h (391 nmol/24 h); normal, 6.6–73 μg/24 h (18.8–209 nmol/24 h)]; and marked increases in tetrahydro-18-hydroxy-11-deoxycorticosterone [33.42 μg/24 h (95.5 nmol/24 h); normal, 0.6–3.2 μg/24 h (1.7–9.1 nmol/24 h)] and tetrahydro-11-dehydrocorticosterone [110.1 μg/24 h (316 nmol/24 h); normal, 5.2–31 (15–89 nmol/liter)]. Urinary metabolite ratios of B/18OHB and 18OHB/aldosterone were intermediate between those in ASD type I and type II (Table 1).

At 8 and 16 months of age, fludrocortisone was stopped for 1 wk to perform further hormonal assays. Plasma aldosterone levels were 1.4 and 4.3 ng/dl (38.8 and 119.3 pmol/

TABLE 1. Urinary tetrahydrosteroid metabolite levels measured by gas chromatography-mass spectrometry

	ALDO THmetab (μg/24 h)	18OHB THmetab (μg/24 h)	B THmetab (μg/24 h)	18OHB/ALDO metabolite ratio	B/18OHB metabolite ratio
Patient	4.6	18.2	257.17	3.96	14.13
ASD 1 patients	0	42.9 ± 25.1	2,870 ± 735	∞	84 ± 36
ASD 2 patients	7.67 ± 4.87	1,590 ± 1,090	2,930 ± 1,250	207 ± 106	1.76 ± 0.86
Normal subjects	0.2–20	3–20	13.8–117	3.34 ± 1.28	7.8 ± 3.1

THmetab, Tetrahydrometabolites; ALDO, aldosterone. Data were collected at 8 wks of age after interruption of sodium supplementation for 24 h. Controls are age-matched.

TABLE 2. Plasma steroid levels measured by RIA

	ALDO (ng/dl)	18OHB (ng/dl)	B (μg/dl)	18OHB/ALDO	B/18OHB
Patient	4.3	67.7	4.6	15.7	14.7
ASD 1 patients	<3	2.3–16	0.7–5.3	N.A.–6	>40
ASD 2 patients	<3–normal	438–2,090	0.7–5.3	>100	<10
Normal subjects	5–60	12–55	0.1–1		

ALDO, Aldosterone. To convert to Systeme International units: ALDO (ng/dl) × 27.74 = pmol/liter; 18OHB (ng/dl) × 27.59 = pmol/liter; B (μg/dl) × 28.87 = nmol/liter. N.A., Not applicable.

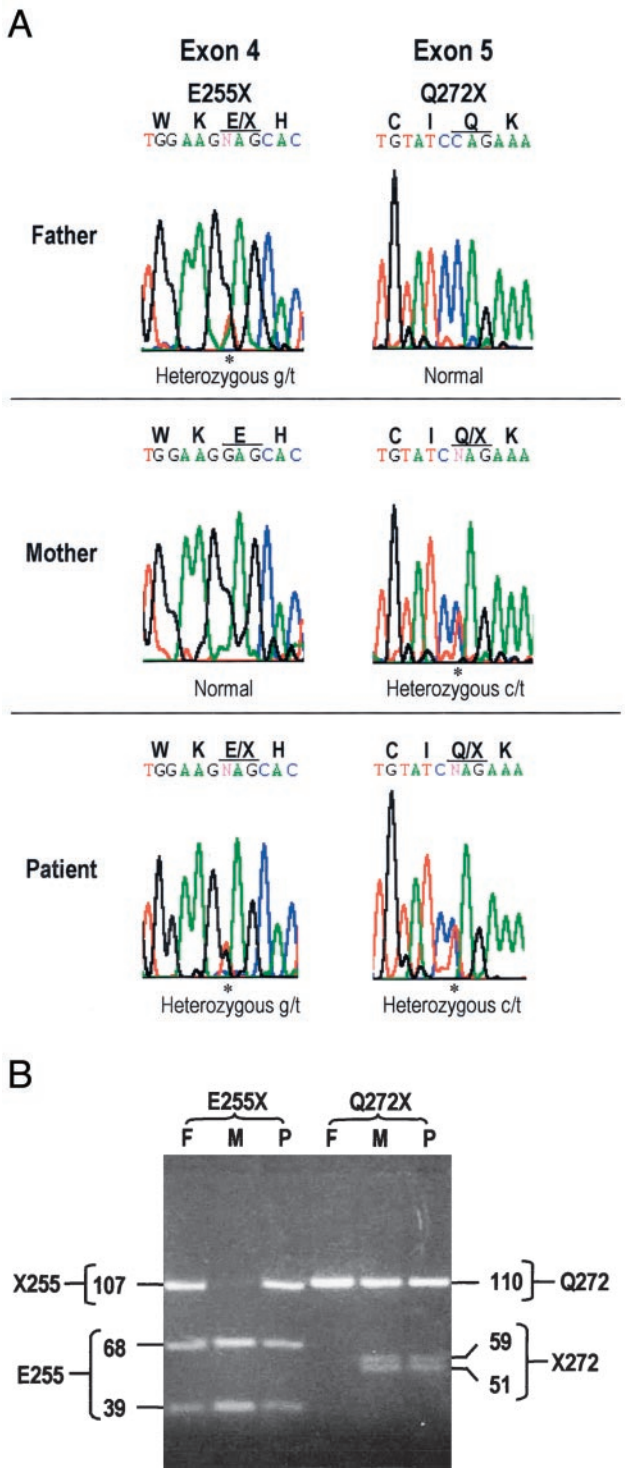

FIG. 1. Heterozygous mutations detected in CYP11B2. A, Direct sequencing of PCR products. Exons 1–5 were amplified from the genomic DNA of the patient and both parents. The PCR products were purified and sequenced by automated direct sequencing. Heterozygous mutations are marked by an *asterisk*. The patient is a compound heterozygote: an E255X mutation in exon 4 was inherited from the father, and a Q272X mutation in exon 5 was inherited from the mother. Therefore, both *CYP11B2* alleles of the patient carry a premature stop codon. The E255X mutation has been described previously (20). B, Restriction digestion of PCR fragments. PCR products of exons 1–5 were used as templates in a second PCR to amplify small fragments of either exon 4 (107 bp) or exon 5 (110 bp) that were incubated with *Sdu*I or *Xba*I, respectively. The E255X mutation in exon 4 destroys an *Sdu*I restriction site. This confirms that the father (F) and the patient (P) are both heterozygous for the mutation, because they display the *Sdu*I-digested normal allele (E255; 68 and 39 bp) in addition to the undigested allele carrying the mutation (X255; 107 bp). Conversely, the mother (M) displays only the normal E255 allele. The Q272X mutation in exon 5 creates an *Xba*I restriction site. The mother and patient are heterozygous for this mutation, because they carry both the *Xba*I-digested mutated allele (X272; 59 and 51 bp) and the undigested normal allele (Q272; 110 bp). In contrast, the father displays only the normal Q272 allele.

liter), and plasma active renin levels were 551 and 1669 ng/liter (332 and 1005 mU/liter), respectively. At 16 months, plasma 18OHB was 67.7 ng/dl [1867.8 pmol/liter; normal range, 12–55 ng/dl (331.1–1517.5 pmol/liter)], and plasma B was 4.6 μg/dl [132.8 nmol/liter; normal range, 0.1–1.0 μg/dl (2.9–29.0 nmol/liter)]. Again, the ratios of B/18OHB and 18OHB/aldosterone were not typical of either ASD type 1 or 2 (Table 2).

Binding studies

The affinity of aldosterone for its receptor in HML was normal (2.7 nmol/liter; normal range, 1.8–3.5), whereas the number of the binding sites was markedly increased (3300 sites/cell; normal range in healthy controls of the same age, 166 ± 66). Interestingly, in adult patients with Addison's disease the number of sites per cell has been shown to be much lower (237 ± 71) (19), similar to that in normal controls of the same age (290 ± 108).

Molecular genetics

Direct sequencing of all nine exons of *CYP11B2* of the patient revealed an heterozygous g/t mutation in exon 4 affecting codon 255 (GAG→TAG) that encodes a premature stop codon instead of a glutamate residue (E255X; Fig. 1A). This mutation has been described previously in the homozygous state in a patient who presented as a newborn with salt-wasting and failure to thrive (20). The sequencing of *CYP11B2* of the patient identified a further heterozygous c/t mutation in exon 5 that affects codon 272 (CAG→TAG) and also results in a premature stop codon instead of a glutamine residue (Q272X). This mutation has not been previously described. Sequencing *CYP11B2* exons 4 and 5 of the patient's father and mother demonstrated that the father was heterozygous for the E255X mutation in exon 4, and exon 5 was normal; conversely, the mother was heterozygous for the Q272X mutation in exon 5, and exon 4 was normal (Fig. 1A). These genotypes were confirmed by restriction enzyme digests (Fig. 1B). Thus, both alleles of *CYP11B2* of the patient carry mutations encoding premature stop codons that are located before critical active site residues of the aldosterone synthase enzyme encoded by *CYP11B2* (21).

Discussion

The case reported in this study highlights the complex genotype-phenotype relationship in patients with ASD. Patients with ASD1 are expected to have CYP11B2 alleles car-

rying deleterious mutations that abolish all CYP11B2 activities *in vitro*. Consequently, the B and 18OHDOC produced by CYP11B1 become the terminal steroids. As a result of the stimulation of CYP11B1 gene expression in the zona glomerulosa by the increased angiotensin II, B and 18OHDOC are produced in excess (1, 22). The secretion of 18OHB produced by CYP11B1 will also increase, but due to the loss of CYP11B2 activity, the overall production of 18OHB is lower, resulting in an increased B/18OHB ratio. Conversely, patients with ASD2 display genetic alterations encoding CYP11B2 enzymes that convert DOC to B, *i.e.* they have efficient 11β-hydroxylase activity, but markedly reduced or ablated 18-hydroxylase and oxidase activities *in vitro*. In this case, CYP11B1 is again up-regulated by the increased angiotensin II, but the excess 18OHDOC can be converted to 18OHB by the 11β-hydroxylase activity of the CYP11B2 enzyme (22), resulting in an increased 18OHB/aldosterone ratio and a decreased B/18OHB ratio.

The patient presented in this study displays a hormonal pattern that is not clearly classifiable as one of the classical ASD forms. In fact, both plasma and urinary aldosterone levels are in the low-normal range, a feature seen more frequently in ASD2 patients. The possibility of a low degree of cross-reactivity in the RIA (18), which would give low levels of aldosterone even when it is absent, can be excluded in our study by the gas chromatography-mass spectrometry measurements of urinary steroid metabolites. Further, this patient displays higher levels of 18OHB than patients with typical ASD1, but not as high as patients with ASD2, resulting in 18OHB/aldosterone and B/18OHB ratios intermediate between the two classical forms. What is of particular interest is the source of low-normal levels of aldosterone in our patient who carries both CYP11B2 alleles with premature stop codons (in exon 4 or 5), which is in contrast to a patient described by Peter *et al.* (23) who was homozygous for the premature stop codon in exon 4 (E255X) and displayed clinical features typical of ASD1. The encoded aldosterone synthase enzymes in our patient should be inactive because they are truncated and lack about half of the enzyme structure, including the residues important for 18-hydroxylase and oxidase activities (amino acids 288 and 320) (21), the putative heme -binding site at position 461 (5), and most of the I helix.

The abnormal mineralocorticoid receptor concentration in mononuclear leukocytes in our infant patient, even compared with those in adult patients with Addison's disease, can be accounted for by the differential requirement for aldosterone between infants and adults; in fact, severely ill children with ASD who have dehydration and progress to shock, become asymptomatic as adults (24). It is conceivable that with the maturation of the kidney and with an increase in sodium intake, there is a decreased requirement for aldosterone to maintain sodium conservation.

In conclusion, we have described an ASD patient with a CYP11B2 gene that carries differential premature stop codons in each allele, predicting the formation of truncated and inactive aldosterone synthase enzymes. However, the patient presents a phenotype intermediate between those of ASD1 and ASD2, rather than the classical ASD1. Further studies are required to identify all of the genes involved in ASD and the regulatory sequences that influence the complex genotype-phenotype of this disease.

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