sciendo

ENDOCRINE REGULATIONS, Vol. 54, No. 3, 227–229, 2020



doi:10.2478/enr-2020-0025

# Aldosterone synthase deficiency type II: an unusual presentation of the first Greek case reported with confirmed genetic analysis

Stayroula Papailiou[1], Elpis Athina Vlachopapadopoulou[2], Amalia Sertedaki[3], Despoina Maritsi[1], Nikolaos Syggelos[1], Angeliki Syggelou[1]

*[1]Second Department of Paediatrics, Children's Hospital 'P. & A. Kyriakou, National and Kapodistrian University of Athens, Athens, Greece; [2]Department of Endocrinology, Growth and Development, 'P. & A. Kyriakou Children's Hospital, Athens, Greece; [3]Division of Endocrinology, Metabolism and Diabetes, First Department of Pediatrics, National and Kapodistrian University of Athens Medical School, 'Aghia Sophia' Children's Hospital, Athens, Greece*
*E-mail: valia.papailiou@gmail.com*

**Objective.** Aldosterone synthase deficiency (ASD) is a rare, autosomal recessive inherited disease with an overall clinical phenotype of failure to thrive, vomiting, severe dehydration, hyperkalemia, and hyponatremia. Mutations in the CYP11B2 gene encoding aldosterone synthase are responsible for the occurrence of ASD. Defects in CYP11B2 gene have only been reported in a limited number of cases worldwide. Due to this potential life-threatening risk, comprehensive hormonal investigation followed by genetic confirmation is essential for the clinical management of offsprings.

**Case presentation.** We herein describe an unusual case of ASD type II in a neonate with faltering growth as a single presenting symptom. To our knowledge, this is the first Greek case of ASD type II reported with confirmed genetic analysis. Next generation sequencing of her DNA revealed the homozygous mutation p.T185I (ACC-ATC) (c.554C>T) (g.7757C>T) in exon 3 of the CYP11B2 gene in the neonate, inherited from both parents who were heterozygotes for the mutation.

**Conclusions.** Physicians handling neonates with faltering growth, particularly in the initial six weeks of life, should be suspicious of mineralocorticoid insufficiency either as isolated hypoaldosteronism or in the context of congenital adrenal hyperplasia. Essential investigations should be performed and appropriate treatment should be administered promptly without awaiting for the hormonal profile results. Interpretation of the clinical picture and the hormonal profile will guide the analysis of candidate genes. Primary selective hypoaldosteronism is a rare, life threatening disease, but still with an unknown overall population impact. Thus, reporting cases with confirmed gene mutations is of major importance.

**Key words:** aldosterone, CYP11B2 gene, hyponatremia, hyperkalemia, metabolic acidosis, faltering growth

Infants with aldosterone synthase deficiency (ASD) type II may develop symptoms of mineralocorticoid deficiency and clinical manifestations may vary with age, including frequent vomiting, a variable degree of electrolytes imbalance, and metabolic acidosis combined with poor growth (Bizzarri et al. 2016). These symptoms may be easily correlated with several other endocrinopathies, including hypoaldosteronism, pseudohypoaldosteronism, and congenital adrenal hyperplasia (Kayes-Wandover Tannin et al. 2001). Aldosterone's production is primarily regulated by plasma renin that stimulates its synthesis through several steps of enzymatic reactions (Hattangady et al. 2012). The three final steps

**Corresponding author:** Dr. Stayroula Papailiou, M.D., Second Department of Pediatrics, 'P. & A. Kyriakou' Children's Hospital, National and Kapodistrian University of Athens (NKUA), Thivon and Livadias Str, Goudi, 11526, Athens, Greece; phone: +302132009468, e-mail: valia.papailiou@gmail.com.

are catalyzed by aldosterone synthase. This is a mitochondrial cytochrome P450 enzyme, encoded by the CYP11B2 gene, located on chromosome 8. The two forms of isolated aldosterone synthase described in literature are corticosterone methyl oxidase type I (CMO I) and type II (CMO II). Corticosterone methyl oxidase type I affects the 18-hydroxylation of corticosterone and CMO II the 18-oxidation of 18-OH corticosterone and finally aldosterone. Mutations in the CYP11B2 gene, both inherited and de novo are an important research challenge in gene discovery (Jessen et al. 2012; Klomchan et al. 2012). Herein, we describe an unusual presentation of the first Greek case of ASD type II reported in a neonate with faltering growth as a single symptom.

## Case presentation

**Subject.** A 23-day old Greek baby girl was referred to our Emergency Department due to failure to thrive. The neonate was the second born child of unrelated parents. Family history is unremarkable. She was born at 38 weeks with normal birth weight (2 990 g), birth length 51 cm and head circumference 33 cm. The immediate perinatal period was uneventful. She was referred by her pediatrician due to very poor weight gain, precisely 60 g since birth. The infant was feeding with formula. Her mother reported that she was a poor feeder but she had no vomiting or diarrhea. On admission, she was active, alert, mildly dehydrated as evidenced by dry mucosae and mild tachycardia (HR: 178/min). Blood pressure was within normal range for her age (89/42 mmHg). There was no ambiguity of her external genitalia or hyperpigmentation noted.

**Biochemistry and endocrine investigation.** The clinical examination was followed by evaluation of venous blood gases and plasma electrolyte concentration. Serum biochemistry abnormalities included high urea (66 mg/dl), high potassium (8 mEq/L), low sodium (122 mEq/L) and metabolic acidosis while urine electrolytes were indicative of excessive natriuresis.

The initial management consisted of intravenous fluid therapy to restore intravascular volume and correct acidosis with rapid administration of 20 ml/kg of isotonic crystalloid deficit replacement, provision of maintenance fluids, and replacement of ongoing losses. Moreover, the additional sodium deficit was calculated and added to rehydration fluids.

The differential diagnosis included renal organic tubulopathies, adrenal insufficiency, isolated hypoaldosteronism and transient pseudohypoaldosteronism, secondary to pyelonephritis. Urine culture was negative and renal ultrasonography was normal. Endocrine tests including cortisol and its precursors, 17OH progesterone, D4-androstendione, aldosterone, and serum renin were performed. As adrenal insufficiency or hypoaldosteronism were high in the differential diagnosis because there was no evidence of pyelonephritis or tubulopathy, a loading dose of hydrocortisone was administered intravenously followed by a daily dose of 50 mg/m$^2$/d divided in 4 doses. The hormonal profile revealed low levels of aldosterone at 235.4 pg/ml (normal values 300–1900 for neonates) and high serum renin up to 31 ng/ml/h (0.32–1.84) with 17OH progesterone (3.59 ng/ml, normal values 0.7–2.5), D4-androstendione (0.57 ng/ml, 0.1–2.99) and serum cortisol (18.46 μg/dl) in the normal range for age.

Due to low serum aldosterone and high serum renin without corresponding changes in cortisol levels, the diagnosis of congenital hyperreninemic hypoaldosteronism was established. Oral fludrocortisone was added to her treatment with simultaneous decrease of hydrocortisone. Oral 15% NaCl was also added in her feeds. The response to treatment was excellent with normalization of electrolyte profile, improvement of appetite and weight gain. She was discharged home at 37 days of life with a weight of 3 810 g. The patient maintains regular follow-up visits to endocrinology clinics and good clinical effect on body growth and psychomotor development.

**Gene sequencing analysis.** Gene sequencing analysis of both parents and neonate revealed a previously known mutation, in the gene CYP11B2 encoding aldosterone synthase (Miaoa et al. 2019). The homozygous mutation p.T185I (ACC-ATC) (c.554C>T) (g.7757C>T) was detected in the exon 3 of the CYP11B2 gene in the neonate, constituting an inherited and not de novo mutation as resulted from both parents' similar heterozygous genotype. Genetic counselling was planned in case of future pregnancies.

## Discussion

This case report refers to the first Greek neonate reported with ASD type II and a rare mutation in the CYP11B2 gene where faltering growth was the single symptom and no major clinical signs were detected on admission. Hyponatremia is a frequent electrolyte disturbance in neonates. Salt-wasting in newborns and infants may result in life threatening complications and mortality is higher in infants with hyponatremia (Storey et al. 2019). The combi-

nation of failure to thrive with hyponatremia and hyperkalemia sets high suspicion for congenital adrenal hyperplasia, hypoaldosteronism or pseudohypoaldosteronism. The absence of ambiguous genitalia with no evidence of urine infection and normal kidney ultrasonography supports the diagnosis of isolated hypoaldosteronism. The incidence of isolated hypoaldosteronism is estimated to be <1:1 000 000. Genetic defects in CYP11B2 cause isolated hypoaldosteronism and are inherited through the autosomal recessive mode (Turan et al. 2018). Our infant had the homozygous mutation p.T185I (ACC-ATC) (c.554C>T) (g.7757C>T) in the exon 3 of the CYP11B2 gene which is consistent with type 2 isolated hypoaldosteronism. The clinical presentation does not differ between type 1 and 2. They only differ in the levels of 18-hydoxycorticosterone (Miaoa et al. 2019).

Physicians treating infants with salt wasting of suspected endocrine origin should bear in mind that the essential hormonal investigations should be performed urgently before starting steroid therapy, but without delaying the initiation of therapy in order to clarify the diagnosis and guide the analysis of candidate genes. Awareness about clinical presentation of ASD will help physicians to identify patients at risk and proceed in a timely diagnosis. Molecular genetic investigations can help unequivocally diagnose these conditions.

## Learning points

- Faltering growth in neonates may be a single alarm sign for endocrine disorders even in the absence of other clinical signs.
- Gene mutation analysis is essential for confirmation of diagnosis and future pregnancy plans.
- Mutations in the CYP11B2 gene, both inherited and de novo are an important research challenge in gene discovery, as the overall prevalence of the disease is still unknown.

## Acknowledgements

We wish to thank all our pediatric colleagues who participated in this work.

## References

Bizzarri C, Olivini N, Pedicelli S, Marini R, Giannone G, Cambiaso P, Cappa M. Congenital primary adrenal insufficiency and selective aldosterone defects presenting as salt-wasting in infancy: a single center 10-year experience. Ital J Pediatr 42, 73, 2016.

Hattangady NG, Olala LO, Bollag WB, Rainey WE. Acute and chronic regulation of aldosterone production. Mol Cell Endocrinol 350, 151–162, 2012.

Jessen CL, Christensen JH, Birkebaek NH, Rittig S. Homozygosity for a mutation in the CYP11B2 gene in an infant with congenital corticosterone methyloxidase deficiency type II. Acta Pædiatrica 101, e519–e525, 2012.

Kayes-Wandover Tannin GM, Shulman D, Peled D, Jones KL, Karaviti L, White PC. Congenital hyperreninemic hypoaldosteronism unlinked to the aldosterone synthase (CYP11B2) gene. J Clin Endocrinol Metab 86, 5379–5382, 2001.

Klomchan T, Supornsilchai V, Wacharasindhu S, Shotelersuk V, Sahakitrungruang T. Novel CYP11B2 mutation causing aldosterone synthase (P450c11AS) deficiency. Eur J Pediatr 171, 1559–1562, 2012.

Miaoa H, Yub Z, Lua L, Zhua H, Auchusc RJ, Liuc J, Jiangd J, Pana H, Gonga F, Chena S, Lua Z. Analysis of novel heterozygous mutations in the CYP11B2 gene causing congenital aldosterone synthase deficiency and literature review. Steroids 150, 108448, 2019.

Storey C, Dauger S, Deschenes G, Heneau A, Baud O, Carel JC, Martinerie L. Hyponatremia in children under 100 days old: incidence and etiologies. Eur J Pediatr 178, 1353–1361, 2019.

Turan I, Kotana D, Tastana M, Gurbuza F, Topaloglua AK, Yuksela B. Molecular genetic studies in a case series of isolated hypoaldosteronism due to biosynthesis defects or aldosterone resistance. Clin Endocrinol (Oxf) 88, 799–805, 2018.