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Rare causes of congenital adrenal steroidogenesis disorders presenting in the neonatal period: clinical picture, diagnostic challenges, and treatment – a report of three cases and a literature review

Rzadkie przyczyny wrodzonych zaburzeń steroidogenezy nadnerczowej ujawniające się w okresie noworodkowym: obraz kliniczny, trudności diagnostyczne i leczenie – opis trzech przypadków i przegląd literatury

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Abstract

Congenital adrenal steroidogenesis disorders are rare diseases that can lead to life-threatening conditions in newborns, primarily salt-wasting syndrome and adrenal crisis. It is therefore essential for paediatricians and family physicians to be familiar with the symptoms suggestive of steroidogenesis defects, such as failure to thrive, vomiting, dehydration, electrolyte imbalances, and abnormal appearance of external genitalia. Early initiation of diagnostic procedures enables the prompt introduction of appropriate hormonal replacement therapy. However, the diagnostic process is not straightforward and requires consideration of other rare causes of the disease, which often present with similar but diverse clinical, biochemical, and hormonal features. A normal result of a screening test assessing 17-hydroxyprogesterone levels does not rule out rare causes of steroidogenesis disorders, which should be considered in the differential diagnosis when the aforementioned symptoms are present. This report discusses three newborns: one diagnosed with congenital adrenal hyperplasia due to 11β-hydroxylase deficiency, and two with aldosterone synthase deficiency.

Keywords: congenital adrenal hyperplasia, hypoaldosteronism, failure to thrive

Streszczenie

Wrodzone zaburzenia steroidogenezy nadnerczowej to choroby rzadkie, które w okresie noworodkowym mogą prowadzić do stanów zagrożenia życia, przede wszystkim zespołu utraty soli i przełomu nadnerczowego. Z tego powodu niezwykle ważna dla pediatry i lekarza rodzinnego jest znajomość objawów sugerujących defekty steroidogenezy, w tym brak przyrostu masy ciała, wymioty, odwodnienie, zaburzenia elektrolitowe i nieprawidłowy wygląd zewnętrznych narządów płciowych. Wczesne wysunięcie podejrzenia i rozpoczęcie diagnostyki umożliwiają szybkie wdrożenie odpowiedniej substytucji hormonalnej. Sama diagnostyka nie jest jednak łatwa i wymaga uwzględnienia innych rzadkich przyczyn choroby, często o zbliżonym, a mimo to różnorodnym, obrazie klinicznym, biochemicznym i hormonalnym. Prawidłowy wynik badania przesiewowego oceniającego stężenie 17-hydroksyprogesteronu u noworodków nie pozwala jednak wykluczyć rzadkich przyczyn zaburzeń steroidogenezy i należy je uwzględniać w diagnostyce różnicowej przy obecności wymienionych objawów. W pracy przedstawiono przypadki trojga noworodków: u jednego rozpoznano wrodzony przerost nadnerczy wynikający z niedoboru 11β-hydroksylazy, a u dwóch – niedobór syntazy aldosteronu.

Słowa kluczowe: wrodzony przerost nadnerczy, hipoaldosteronizm, brak przyrostu masy ciała

INTRODUCTION

The adrenal cortex is the site of biosynthesis for three primary groups of cholesterol-derived hormones: mineralocorticoids (MCs), glucocorticoids (GCs), and adrenal androgens. Each class of corticosteroid is produced in a distinct zone and is subject to different regulatory mechanisms. Aldosterone synthesis in the zona glomerulosa is regulated by the renin–angiotensin–aldosterone system, whereas glucocorticoid production in the zona fasciculata and adrenal androgen synthesis in the zona reticularis are controlled by the hypothalamic–pituitary–adrenal axis via corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH). The production of hormones in each layer of the adrenal cortex involves numerous enzymatic reactions, each of which may be a potential site for blockade[1,2].

Congenital disorders of adrenal steroidogenesis are a group of conditions resulting from mutations in genes encoding one of several enzymes involved in the synthesis of GCs and MCs or in the interconversion of steroids. The vast majority of cases manifest as congenital adrenal hyperplasia (CAH), which is caused by inactivating mutations in the genes encoding enzymes (or their cofactors) involved in cortisol biosynthesis[3]. Reduced cortisol synthesis, and the consequent loss of negative feedback at the hypothalamic and pituitary levels, lead to a secondary increase in CRH and ACTH production, resulting in adrenal hyperplasia and the accumulation of hormonal precursors proximal to the enzymatic block. Depending on the site of steroidogenic blockade and the degree of enzyme deficiency, cortisol deficiency may coexist with an excess or deficiency of mineralocorticoids and/or adrenal androgens. In 90–95% of cases, CAH is caused by reduced 21α-hydroxylase activity (due to mutations in the *CYP21A2* gene), whereas in 2–5% of cases it is caused by 11β-hydroxylase deficiency (due to mutations in the *CYP11B1* gene)[3]. A much rarer disorder of adrenal steroidogenesis is aldosterone synthase deficiency (ASD), which is caused by mutations in the *CYP11B2* gene and presents with isolated hypoaldosteronism alongside normal cortisol and ACTH levels[4].

The clinical manifestations of congenital disorders of adrenal steroidogenesis in the neonatal period are non-specific and depend on the sex of the neonate, the stage of steroidogenesis affected, and the degree of enzyme impairment. MC deficiency (whether isolated or associated with GC deficiency) may result in failure to thrive, vomiting, and dehydration, with biochemical tests often revealing hyponatraemia and hyperkalaemia, whereas an excess may result in arterial hypertension. Elevated levels of adrenal androgens in the female foetus may cause virilisation of the external genitalia, whereas in the male foetus they do not usually result in significant abnormalities. However, adrenal androgen deficiency in male foetuses may result in incomplete masculinisation of the external genitalia. Cortisol deficiency may lead to hypoglycaemia, and an excess of ACTH precursors may cause hyperpigmentation of the skin, although this parameter is somewhat subjective[1].

In Poland, neonatal screening for CAH is primarily aimed at detecting steroid 21α-hydroxylase deficiency, in which cortisol deficiency coexists with excess adrenal androgens and aldosterone deficiency. In this screening programme, 17-OH progesterone (17-OHP) levels are measured and, if elevated, a steroid profile is obtained[5]. Other disorders of adrenal steroidogenesis are not routinely screened for in this programme.

The extended diagnostic evaluation for disorders of adrenal steroidogenesis includes hormonal assays – such as measurements of 17-OHP, cortisol, ACTH, and aldosterone – as well as assessments of plasma renin activity (or renin concentration) and adrenal androgen levels. These investigations should be carried out on blood samples taken before the start of hormone therapy[4]. A urinary steroid profile is also recommended, and genetic testing is particularly useful to confirm the diagnosis.

This article discusses rare disorders of adrenal steroidogenesis, specifically 11β-hydroxylase deficiency – the second most common form of CAH – and ASD.

CASE REPORTS

Patient 1

A female infant from a primigravida and primiparous pregnancy, delivered by caesarean section at 39 weeks' gestation due to failure to progress, was born with a birth weight of 3,450 g, a length of 57 cm, and an Apgar score of 10. At seven days of age, she was referred to the Paediatric Endocrinology Department on suspicion of CAH, based on virilisation of the external genitalia and an elevated 17-OH progesterone (17-OHP) level detected by fluorometric screening (17-OHP: 45.45 nmol/L, normal: <26.1 nmol/L). On admission, the girl was in good general condition, without signs of dehydration, with a weight of 3,500 g and normal blood pressure (BP measurements: 64/46 mm Hg, 82/52 mm Hg, 92/55 mm Hg, 106/62 mm Hg, 86/46 mm Hg; the 95th percentile for 40 weeks' gestation is 95/65 mm Hg). Physical examination revealed markedly increased pigmentation of the areolae and labial skin, and virilisation of the external genitalia (Prader's stage III: markedly enlarged clitoris, partially fused labia, with the vagina and urethra opening into a common urogenital sinus). The screening steroid profile from a dried blood spot, along with laboratory tests carried out in the department, are shown in Tab. 1. A diagnosis of 11β-hydroxylase deficiency was suspected based on the virilisation of the external genitalia, the elevated 17-OHP level in the screening, and the elevated 11-deoxycortisol level in the steroid profile. Genetic testing revealed a pathogenic variant p.Arg448His (c.1343G>A) in both alleles of the *CYP11B1* gene in a homozygous configuration. On the first day of hospitalisation, hydrocortisone was initiated at a dose of 20 mg/m^2 per day, divided into four doses,

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Fluorometric 17-OHP screening assay		
Test	**Result**	**Normal range**
17-OHP [nmol/L]	**45.45**	<26.1
Dried blood spot steroid profile screening		
17-OHP [nmol/L]	7.39	0.1–14.8
Cortisol [nmol/L]	**4.80**	11–4569
11-deoxycortisol [nmol/L]	**682.0**	<85.2
21-deoxycortisol [nmol/L]	**65.30**	<5.9
Androstenedione [nmol/L]	**76.00**	1.75–32.65
Tests performed on admission (6th day of life, before starting GC therapy)		
Sodium [Na, mmol/L]	141	135–145
Potassium [K, mmol/L	5.3	3.2–5.5
Cortisol [µg/dL]	5.9	3.7–19.4 (until 10:00 am)
ACTH [pg/mL]	**567**	Do 46
Renin concentration [µIU/mL]	**173.8**	2.8–39.9 (at rest)
Aldosterone [ng/mL]	–	–
17-OHP [ng/mL]	**22.3**	–
Androstenedione [ng/mL]	**10**	0.3–3.3
DHEAS [µg/dL]	**128**	–
Tests performed at discharge, during glucocorticoid therapy (13th day of life)		
Sodium [Na, mmol/L]	136	135–145
Potassium [K, mmol/L]	6	3.4–6
Renin concentration [µIU/mL]	**>500**	2.8–39.9 (at rest)
17-OHP – 17-hydroxyprogesterone; **ACTH** – adrenocorticotropic hormone; **DHEAS** – dehydroepiandrosterone sulphate; **GCs** – glucocorticoids.		

Tab. 1. Laboratory results in a girl with 11β-hydroxylase deficiency (patient 1)

and good weight gain was observed (3,640 g at discharge). The patient was discharged on day 6 of hospitalisation with recommendations to continue hydrocortisone therapy under electrolyte monitoring. Due to the occurrence of mild hyponatraemia on day 14 of life (Na: 133.9 mmol/L, K: 5.36 mmol/L, Cl: 99.9 mmol/L), fludrocortisone was started temporarily and discontinued after two months of therapy. The child is currently showing normal weight gain.

Patient 2

A male infant was born to a primigravida and primiparous pregnancy at 38 weeks' gestation, with a birth weight of 3,100 g and an Apgar score of 10. On day 8 of life, weighing 2,730 g, the infant was admitted to the Neonatology Unit due to failure to thrive and a tendency to regurgitate. The results of screening tests were normal. A review of the family history revealed that the child's father had experienced salt-wasting syndrome during the neonatal period. Based on the urinary steroid profile, CAH was excluded, and primary adrenal insufficiency was diagnosed. The child's father had been treated with hydrocortisone and fludrocortisone, with substitution therapy discontinued at 13 years of age.

At admission, the neonate's condition was described as moderate. Features of hypotrophy and dehydration were noted (a weight loss of 370 g from birth – approximately 12%), along with excessive scrotal pigmentation and clear heart sounds. Laboratory investigations at that time revealed hyperkalaemia (K: 7.6 mmol/L, normal: 3.5–5.1), hypotonic hyponatraemia (Na: 128.1 mmol/L, normal: 135–148; plasma osmolality: 239 mOsm/kg H_2O, normal: 280–295), and hyperbilirubinaemia. The cortisol level prior to the initiation of hydrocortisone therapy was 7.1 µg/dL and considered within normal limits. Following consultation with a paediatric endocrinologist, treatment with hydrocortisone, an infusion of 3% sodium chloride solution, and salt supplementation of feeds was initiated. On the 13th day of life, the patient was transferred to the Paediatric Endocrinology Department for further diagnostics and treatment. At that time, the patient was in good general condition without signs of dehydration, and his weight was 3,222 g. The laboratory test results are presented in Tab. 2. Additionally, the urinary steroid profile excluded CAH but suggested observation for ASD. Elevated renin levels accompanied by an inappropriately low aldosterone level (the test was performed during hydrocortisone therapy and infusion of 3% sodium chloride solution), along with a positive family

Test	Result	Normal range
Tests performed upon admission to the Neonatology Unit (8th day of life, before initiation of GC therapy)		
Sodium [Na, mmol/L]	128–124	135–148
Potassium [K, mmol/L]	7.6	3.5–5.1
Sodium in urine sample [mmol/L]	33.4	–
Cortisol [µg/dL]	7.1	4.82–19.5
Initial hospitalisation (14th day of life, 7th day of hydrocortisone treatment)		
Sodium [Na, mmol/L]	135	135–145
Potassium [K, mmol/L]	4.6	3.4–6.0
Cortisol [nmol/L]	–	–
ACTH [pg/mL]	–	–
Renin concentration [µIU/mL]	**122.1**	2.8–39.9 (at rest)
Aldosterone [ng/mL]	3.04	1.76–23.2 (at rest)
Aldosterone in 24-hour urine collection [µg/24 h]	**0.16**	1.19–28.1
Total bilirubin [mg/dL]	**5.2**	0.2–1.2
Follow-up visit (7th week of life)		
Sodium [Na, mmol/L]	139	135–145
Potassium [K, mmol/L]	4.9	3.4–6.0
Aldosterone [ng/mL]	5.82	1.76–23.2 (at rest)
Follow-up visit (age: 3.5 months)		
Sodium [Na, mmol/L]	138	135–145
Potassium [K, mmol/L]	5.4	3.4–6.0
Renin [µIU/mL]	0.7052	2.8–39.9 (at rest)
ACTH – adrenocorticotropic hormone; **GCs** – glucocorticoids.		

Tab. 2. Laboratory results in a boy with hyperreninaemic hypoaldosteronism without a detected CYP11B2 *gene mutation (patient 2)*

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history, led to the diagnosis of hyperreninaemic hypoaldosteronism. Testing for mutations in the *CYP11B2* gene was ordered. During treatment in the Paediatric Endocrinology Department, under electrolyte monitoring, hydrocortisone was gradually replaced by fludrocortisone at a dose of 100 μg twice daily, and feeds were supplemented with salt up to 1 g per day (10 mL of 10% sodium chloride solution). With this treatment and the recommendation for daily weight monitoring, the child was discharged in good general condition. A follow-up visit occurred after four weeks, during which good weight gain was observed (an increase of 1,190 g since the previous visit), and sodium and potassium levels were found to be normal (Tab. 2). Genetic testing did not reveal any pathogenic mutations in the *CYP11B2* gene. However, it should be noted that another mechanism leading to damage of both copies of the gene is possible, such as intragenic rearrangements. Given the clinical improvement with the current treatment, the absence of symptoms suggesting cortisol deficiency and/or excess adrenal androgens, and the hereditary nature of the condition in the child, ASD remains the suspected diagnosis.

Patient 3

A male infant from a secundigravida, secundiparous pregnancy was born with a birth weight of 2,950 g and an Apgar score of 10. During the neonatal period, the infant presented with hypotonia, failure to thrive, and a tendency to regurgitate. Laboratory investigations revealed hyponatraemia and intermittent hyperkalaemia. During hospitalisation in the Neonatal Pathology Unit, neurological, cardiological, ophthalmological, genetic, and metabolic investigations were carried out. Due to persistent failure to gain weight, a gastrostomy was performed. At 10 weeks of age, the infant was transferred to the Paediatric Endocrinology Clinic for further evaluation of persistent hyponatraemia, periodic hyperkalaemia, and poor weight gain despite gastrostomy feeding. On admission, the infant was in relatively good condition, with a body weight of 3,650 g. Hypotonia and a flexed hand posture were noted, though there were no obvious signs of dehydration and genital anatomy was normal. The results of the laboratory tests on admission are shown in Tab. 3. CAH was excluded on the basis of the steroid profile from a 24-hour urine collection and normal serum ACTH levels. However, ASD was suspected due to the presence of hyponatraemia, intermittent hyperkalaemia, and elevated renin levels in the context of an inappropriately low aldosterone concentration. Treatment with fludrocortisone and dietary salt supplementation was initiated. Subsequent genetic testing revealed a pathogenic variant p.Thr185Ile (c.554C>T) in both alleles of the *CYP11B2* gene in a homozygous state.

Test	Result	Normal range
Sodium [Na, mmol/L]	**130**	135–145
Potassium [K, mmol/L]	5	3.5–5.6
Cortisol [μg/dL]	25.8	3.7–19.4 (until 10:00 am)
ACTH [pg/mL]	19.2	Up to 46
Renin concentration [μIU/mL]	**>500**	2.8–39.9 (at rest)
Aldosterone [ng/dL]	14.4	1.76–23.2 (at rest)
Urinary cortisol [μg/24 h]	13.6	4.3–176
Sodium and potassium in urine sample [mmol/L]	**63** (Na) and **17.6** (K)	–
ACTH – adrenocorticotropic hormone.		

Tab. 3. Laboratory results in a boy with a confirmed CYP11B2 *gene mutation (patient 3). Tests performed on day 1 of hospitalisation, before initiation of fludrocortisone*

DISCUSSION

Congenital disorders of adrenal steroidogenesis can lead to life-threatening conditions in the neonatal period, particularly adrenal crisis. At the same time, the clinical presentation of these disorders is highly heterogeneous and often non-specific. It is therefore essential to consider steroidogenesis disorders in the differential diagnosis of neonates presenting with alarming symptoms such as failure to thrive, vomiting, dehydration, electrolyte disturbances (hyponatraemia with intermittent hyperkalaemia), and abnormal external genitalia[1,2]. Each of the patients discussed in this article had at least one of these symptoms.

Before the introduction of neonatal screening for 17-OHP, virilisation of the external genitalia in female newborns was associated with a significantly better prognosis in girls with 21α-hydroxylase deficiency. In male neonates, the first manifestation was salt-wasting syndrome, and these infants could often be misdiagnosed as having sepsis or metabolic disorders, sometimes leading to unexplained deaths[6]. Currently, neonatal screening for 17-OHP is performed in Poland to enable the early detection of 21α-hydroxylase deficiency[6]. While an elevated 17-OHP level is the classic, albeit non-specific, marker for this form of CAH, it can also be seen in preterm infants, neonates undergoing evaluation during infection or other stress, and in other rare forms of CAH, including 11β-hydroxylase deficiency[7]. In the event of an abnormal screening result, a confirmatory test is performed in the form of a serum steroid profile, which measures the concentrations of 17-OHP, 11-deoxycortisol, cortisol, 21-deoxycortisol, and androstenedione[5].

The enzyme 21α-hydroxylase is essential for the synthesis of cortisol and aldosterone. It catalyses the conversion of 17-OHP to 11-deoxycortisol and of progesterone to 11-deoxycorticosterone (DOC). The resulting products serve as substrates for the enzyme 11β-hydroxylase, which converts 11-deoxycortisol to cortisol and DOC to corticosterone. In patients with 21α-hydroxylase deficiency, the conversion of 17-OHP to 11-deoxycortisol is impaired, leading to increased levels of 17-OHP. This is metabolised to adrenal androgens and, through the action of 11β-hydroxylase, to 21-deoxycortisol. Therefore, 21-deoxycortisol is

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considered to be a specific marker of 21α-hydroxylase deficiency[8]. In this deficiency, the accumulation of metabolites upstream of the enzymatic block may result in the inhibition of 21α-hydroxylase by high concentrations of 11-deoxycortisol, causing a moderate increase in 17-OHP. Consequently, 11β-hydroxylase deficiency may be detected in newborn screening, prompting further endocrine diagnostics, especially in girls with virilisation features[1]. The symptoms of 11β-hydroxylase deficiency in the neonatal period result from excess androgens, cortisol deficiency, and increased ACTH (manifested as hypoglycaemia and skin hyperpigmentation). In female foetuses, virilisation of the external genitalia can be observed, while the internal genitalia develop normally. In male newborns, androgen excess typically manifests as GnRH-independent isosexual precocious puberty (early pubic and axillary hair, acne, and strong body odour), usually after the third year of life, whereas in the neonatal period only hyperpigmentation of the scrotal and penile skin – secondary to increased ACTH synthesis – is observed[1]. However, the assessment of this sign is subjective and prone to error, as illustrated by the physical examination findings in patient 2. The physician, guided by the signs of salt-wasting syndrome, noted increased skin pigmentation despite the diagnosis of isolated hypoaldosteronism. In untreated or inadequately treated older children, disturbances in sexual development may occur, along with growth disturbances. These children tend to grow rapidly, are inappropriately tall for their chronological age, and have a disproportionately advanced bone age. As a result, they do not reach their growth potential and their final height is low.

In patient 1, the presence of virilisation features on physical examination (enlarged clitoris, partially fused labia) and an initially elevated 17-OHP level on screening provided the basis for further endocrine evaluation. The reduced cortisol concentration and elevated ACTH levels observed in hormonal studies were consistent with the suspicion of CAH. Additionally, the high level of 11-deoxycortisol in the screening steroid profile directed the diagnostic process towards 11β-hydroxylase deficiency, which was confirmed by the presence of a homozygous mutation in the *CYP11B1* gene. However, the elevated level of 21-deoxycortisol in the steroid profile and the high renin concentration are puzzling, as these findings are not typical in 11β-hydroxylase deficiency. The clinical picture of 11β-hydroxylase deficiency is similar to that of 21α-hydroxylase deficiency, except for the excess of mineralocorticoids. 11β-hydroxylase deficiency leads to a significant accumulation of DOC, which exhibits mineralocorticoid activity, preventing the development of salt-wasting syndrome. However, later in life, it may cause sodium retention, arterial hypertension, and sometimes hypokalaemia. These symptoms are not usually observed in newborn infants, but rather in the early years of life due to aldosterone resistance and increased mineralocorticoid requirements in the neonatal period. The transient development of salt-wasting syndrome in this form of CAH may occur with the initiation of hydrocortisone treatment. As a glucocorticoid, hydrocortisone suppresses ACTH secretion via negative feedback, which may result in reduced ACTH-dependent 21α-hydroxylase activity and a subsequent decrease in DOC concentration[1,9]. This mechanism, together with the physiological aldosterone resistance in the neonatal period, may explain the initially elevated renin concentration observed in patient 1 and its further increase after the initiation of hormone therapy. The initial biochemical investigations did not reveal hyponatraemia or hyperkalaemia, which distinguishes this condition from 21α-hydroxylase deficiency with salt wasting. However, mild hyponatraemia developed a few days after the start of hydrocortisone replacement, leading to the temporary introduction of fludrocortisone, which was discontinued after two months of therapy. The selection of appropriate replacement therapy requires an accurate diagnosis prior to treatment. In contrast to the classic salt-wasting form of 21α-hydroxylase deficiency, in which both hydrocortisone and fludrocortisone are administered lifelong, 11β-hydroxylase deficiency can be treated with hydrocortisone alone. Patients with 11β-hydroxylase deficiency should also be informed of an increased risk of cardiovascular complications, such as arterial hypertension[8].

ASD is a disorder caused by inactivating mutations in the *CYP11B2* gene and is characterised exclusively by symptoms associated with mineralocorticoid deficiency, without abnormalities in glucocorticoids and adrenal androgens. In contrast to CAH, normal levels of ACTH and cortisol are observed in ASD. Depending on the residual activity of the enzyme, ASD may present in a mild form with failure to thrive or weight loss, vomiting, hyponatraemia and hyperkalaemia, or in a severe form as rapidly progressing salt-wasting syndrome with dehydration, hypotension, seizures, shock, and ultimately death, if appropriate therapy is not administered. Salt-wasting syndrome does not typically manifest immediately after birth, but rather between the 5th and 14th day of life, due to the involution of the foetal adrenal gland at this time[1,4]. However, ASD is associated with a far lower risk of this dangerous complication than CAH. This is probably due to the preserved synthesis of deoxycorticosterone, corticosterone, and cortisol, which, through some mineralocorticoid activity, provide partial protection against severe salt wasting and shock. Nevertheless, hyponatraemia in ASD can lead to other serious complications, such as growth retardation and delayed intellectual development[2]. In patient 3, the presence of hyponatraemia and intermittent hyperkalaemia raised the suspicion of adrenal steroidogenesis disorders, and the normal levels of ACTH and cortisol allowed for the exclusion of CAH. In this situation, with an elevated renin concentration and an inappropriately low aldosterone level, further investigation for mutations in the *CYP11B2* gene is indicated, which in this case confirmed the diagnosis of ASD. Similar hormonal laboratory findings were observed in patient 2. In addition, clinical and biochemical improvement was noted

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after the initiation of fludrocortisone and salt supplementation. During the neonatal period, the father of patient 2 was diagnosed with salt-wasting syndrome; later in infancy, CAH was excluded based on the urinary steroid profile, and primary adrenal insufficiency was diagnosed, with treatment consisting of hydrocortisone and fludrocortisone. The clinical history of the father, with substitution therapy discontinued at the age of 13 years, also suggests ASD as the correct diagnosis, since in isolated mineralocorticoid deficiency, salt-wasting syndrome tends to resolve spontaneously in adolescence[4,10,11]. In patient 2, genetic testing revealed no pathogenic variants in the *CYP11B2* gene; however, case reports in the literature describe hereditary isolated hyperreninaemic hypoaldosteronism in which no mutations in the *CYP11B2* gene were found. It is suggested that, in such cases, potential disease mechanisms may involve mutations in genes encoding other proteins involved in the regulation of aldosterone biosynthesis (e.g. angiotensin-converting enzyme, angiotensinogen, angiotensin II)[12,13]. The cornerstone of treatment for CAH resulting from both 11β-hydroxylase deficiency and ASD is hormone replacement therapy. 11β-hydroxylase deficiency is treated with hydrocortisone, usually at a daily dose of 10–15 mg/m^2 of body surface area, administered in 3–4 divided doses to mimic the circadian rhythm of cortisol secretion (higher doses in the morning and lower doses in the evening). In the neonatal period, immediately after diagnosis, the daily dose is even higher, amounting to 20–25 mg/m^2 during the first month of life. Replacement therapy also aims to suppress the hyperactive CRH–ACTH–adrenal axis, thereby reducing adrenal androgen production[1]. In ASD, the cornerstone of therapy is fludrocortisone combined with salt supplementation in the feed[4]. It should be noted that hydrocortisone doses are increased during stressful situations (e.g. infections), puberty and growth spurts, whereas fludrocortisone doses remain unchanged in ASD. In both conditions, it is essential to monitor treatment with regular endocrine evaluations, assessments of physical development and pubertal progression, blood pressure measurements, and electrolyte monitoring[1]. As the need for mineralocorticoids decreases with age in some patients with ASD, it may be possible to discontinue hormone replacement therapy later in life[4,10]. An example of this is the father of patient 2, who did not require treatment after the age of 13. The family history of this patient also underlines the importance of thorough diagnosis and accurate identification of adrenal steroidogenesis disorders. Early diagnosis allows prompt initiation of treatment in the offspring if the disease is inherited, thereby preventing the occurrence of acute disorders and ensuring normal child development.

CONCLUSIONS

Congenital disorders of adrenal steroidogenesis manifesting in the neonatal period are associated with numerous health problems. For this reason, it is extremely important to recognise the signs that indicate defects in steroidogenesis. Early suspicion of abnormalities and prompt initiation of diagnostic evaluation enable the rapid implementation of appropriate hormone replacement therapy. However, the diagnostic process itself is challenging and requires consideration of rare aetiologies of the disease, which often present with similar, though distinct, clinical, biochemical, and hormonal profiles. Screening for 17-OH progesterone levels primarily facilitates the detection of 21α-hydroxylase deficiency; however, elevated levels may also be observed in 11β-hydroxylase deficiency. A normal screening result does not exclude other, rarer causes of steroidogenesis disorders, which must therefore be considered in the differential diagnosis. In ASD, a gradual resolution of the symptoms of salt-wasting syndrome is observed, often allowing replacement therapy to be discontinued during adolescence.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

Author contribution

Original concept of study: BS, OD, JP, JC. Collection, recording and/or compilation of data: BS, BS, JC. Analysis and interpretation of data: BS, WB, FG, JP, AG. Writing of manuscript: BS, WB, OD, FG. Critical review of manuscript: RŚ, JC. Final approval of manuscript: RŚ.

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