Diagnosis and Management of Congenital Adrenal Hyperplasia: 20-Year Experience in Songklanagarind Hospital

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Objective: *To describe the types of congenital adrenal hyperplasia (CAH) in Thai children, and the clinical and laboratory findings associated with each type.*
Material and Method: *The medical records of CAH patients, aged 0 to 15 years, were retrospectively reviewed.*
Results: *During the 20-year period (1991-2011), there were 66 CAH patients. The most common type was salt-wasting 21-hydroxylase deficiency (21-OHDSW) (59.1%), followed by simple virilizing 21-hydroxylase deficiency (21-OHDSV) (30.3%), 20, 22-desmolase/steroidogenic acute regulatory protein (20,22D/StAR) deficiency (6.1%), and 3β-hydroxysteroid dehydrogenase (3β-HSD) deficiency (4.5%). The stimulated cortisol level was <18 μg/dL in most patients, with 20 cases of 21-OHDSV having a median level of 19.49 μg/dL. The median basal 17-hydroxyprogesterone (17-OHP) levels were markedly elevated in 21-OHDSW and 21-OHDSV patients (20,264 and 5,985 ng/dL, respectively), but was very low in 20, 22D/StAR deficiency patients (260 ng/dL). Bilateral adrenal enlargement, demonstrated by radioimaging, was helpful for diagnosis of 20,22D/StAR and 3β-HSD deficiency.*
Conclusion: *The most common type of CAH in our population was 21-hydroxylase deficiency. The steroid profile of cortisol, 17-OHP, and testosterone levels is helpful for clinical diagnosis of 21-OH deficiency. The low 17-hydroxyprogesterone and low cortisol levels in phenotypic female infant with salt-wasting crisis suggests the diagnosis of 20, 22D/StAR deficiency CAH.*

Keywords: *Adrenal crisis, Adrenal insufficiency, Ambiguous genitalia, Congenital adrenal hyperplasia, Precocious pseudopuberty*

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Congenital adrenal hyperplasia (CAH) is a group of inherited autosomal recessive disorders resulting from mutations of various genes that produce enzymes required for the synthesis of cortisol in the adrenal cortex, namely 20, 22-desmolase/ steroidogenic acute regulatory protein (20,22D/StAR), 3β-hydroxysteroid dehydrogenase (3β-HSD), 21-hydroxylase (21-OH), 11-hydroxylase (11-OH), and 17-hydroxylase (17-OH)[1-3]. CAH is a common disease with the incidence rate of 21-OH deficiency, the most common type found in 90 to 95% of all CAH cases, as detected by neonatal screening of 1:10,000-1:23,000[4-8]. The clinical symptoms of CAH vary depending upon the specific enzymatic deficiency and the gender of the patients. The major symptoms are salt-wasting due to inadequate mineralocorticoids leading to dehydration, shock, and death in undiagnosed patients (20,22D/StAR deficiency, 3β-HSD deficiency, and salt-wasting 21-OH deficiency), hypertension due to an excess of mineralocorticoids (11-OH deficiency, 17-OH deficiency), and ambiguous genitalia and virilization in females, with precocious pseudopuberty in the early childhood period due to excessive androgens (simple virilizing 21-OH deficiency)[1-3].

In Thailand, the incidence of CAH is not known since neonatal screening for such disease is not commonly performed[9]. There are only a few studies from Thailand in which CAH is mentioned, and most of these cases were noted in studies of ambiguous genitalia[10] or adrenal insufficiency[11]. Songklanagarind Hospital is the major tertiary care institution in southern Thailand. Most cases requiring special care are referred there, including cases of adrenal crisis, sexual ambiguity, and precocious puberty, which are referred for endocrinological

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evaluation for definite diagnosis. It was the authors' purpose to provide data on the clinical features and laboratory and hormonal studies of CAH in children based on the authors' 20 years of experience.

Material and Method

The medical records of patients who were diagnosed with congenital adrenal hyperplasia at Songklanagarind Hospital between January 1991 and December 2011, aged 0 to 15 years, were retrospectively reviewed. Data collection included age at initial presentation, clinical manifestations (dehydration, poor weight gain, skin hyperpigmentation, ambiguous genitalia, presence of pubic hair, growth acceleration, virilization, weight, length/height), blood chemistries (BUN, creatinine, electrolytes), and hormonal studies (cortisol, 17-hydroxyprogesterone (17-OHP), dehydroepiandrosterone sulphate (DHEAS), and testosterone). A chromosomal study was performed in all patients with phenotypic female or ambiguous genitalia or apparent male with hypospadias or undescended testis, but not performed in patients with normal male genitalia with bilateral palpable testes. An abdominal computed tomography (CT) or magnetic resonance imaging (MRI) was performed in patients with the clinical findings of salt-wasting who had a low 17-OHP level, regardless of 46,XX or 46,XY karyotype or phenotypic female, phenotypic male or ambiguous genitalia (in assessing this type of abnormality, a radiological finding of bilateral adrenal enlargement is consistent with the diagnosis of congenital adrenal hyperplasia).

At initial presentation, all patients had their weight and length/height measured. In children aged under 2 years, length was measured in a lying position using an infantometer. For children aged 2 years and over, height was measured in the standing position using a Harpenden stadiometer. Body weight was measured using a beam balance scale. The length/height and weight were expressed in cm and kg, respectively, and were transformed to a standard deviation score (SDS) based on chronological age using growth data of the Thai population as a reference[12]. With patients who presented with salt-wasting crisis, a critical sample was collected for cortisol, 17-OHP, DHEAS and testosterone assays. Patients who were evaluated for the early presence of pubic hair with or without other signs of virilization and growth acceleration were given a 250-microgram adrenocorticotropic hormone (ACTH) stimulation test and blood samples were collected for cortisol and 17-OHP at 0 and 60 minutes. DHEAS and testosterone levels were collected only at 0 minute.

Hormone measurements

Cortisol, testosterone, and DHEAS levels were measured using the chemiluminescent assay method. The lowest detectable levels using this method are 0.02 µg/dL, 0.02 ng/mL and 15 µg/dL for cortisol, testosterone, and DHEAS, respectively. 17-OHP level was measured by radioimmunoassay with which the lowest detectable level is 10 ng/dL.

Statistical analysis

This was a descriptive study. Data were expressed as median and ranges. The Kruskal-Wallis test was used to compare differences of variables between groups. Statistical differences were considered significant at a p-value of <0.05.

The protocol for the present study was approved by the Ethics Committee of the Faculty of Medicine, Prince of Songkla University.

Results

During the 20-year study period, 66 patients were diagnosed with congenital adrenal hyperplasia and included 39 (59.1%) with salt-wasting 21-OH deficiency (21-OHDSW), 20 (30.3%) with simple virilizing 21-OH deficiency (21-OHDSV), four (6.1%) with 20,22D/StAR deficiency, and three (4.5%) with 3β-HSD deficiency (none of the presented patients had 11-OH or 17-OH deficiency). The clinical manifestations of the CAH patients at initial presentation are shown in Table 1. All of the patients with 20,22D/StAR, 21-OHDSW, and 3β-HSD deficiencies presented with clinical findings of dehydration, weight loss or poor weight gain, and hyponatremic hyperkalemic metabolic acidosis, at a median age of 1.8 months (range 0.5-5.5 months). Patients with 21-OHDSV presented with slow or rapid progression of clitoromegaly in girls and increased penile size in boys at a median age of 5 years (range 2.8-8.1 years).

All patients were born at term or near-term with a median birth weight of 3,115 gm (range 2,380-3,670 gm). Significant weight loss was found in all cases with 21-OHDSW, 20,22D/StAR, and 3β-HSD deficiencies, as shown by the decrease in median weight SDS from 0.03 at birth to -1.52 at the median age of 1.8 months. Ambiguous genitalia were found in 16 of 19 girls (84.2%) with 21-OHDSW (clitoromegaly, labial fusion and/or scrotal-like labia), five of 13 girls (38.5%) with 21-OHDSV, and in the

Table 1. Clinical manifestations at initial presentation

	20,22D/StAR (n = 4)	21-OHDSW (n = 39)	21-OHDSV (n = 20)	3β-HSD (n = 3)
Median age (years)	0.14	0.15	5.10	0.15
Genitalia				
Female/female-like	4	3/19	8/13	-
Ambiguous	-	16/19	5/13	1
Male	-	20/20	7/7	2
Weight loss/dehydration	Yes	Yes	No	Yes
Birthweight (kg)	3.02	3.12	3.22	3.15
Birthweight SDS	-0.16	0.03	0.08	0.04
Weight at diagnosis (kg)	3.30	3.22	22.46	3.62
Weight SDS	-2.38*	-1.52*	2.42	-1.31*
Length/height SDS	-0.72*	-0.40*	1.98	-1.03*
Skin hyperpigmentation	4/4	24/35	10/20	3/3
Clitoromegaly	None	16/19 girls	13/13 girls	-
Scrotal-like labia	None	10/19 girls	-/13 girls	-
Presence of pubic hair	-	-	8/13 girls 4/7 boys	-
Phallus length (cm)	-	2.63 (19 girls) 3.87 (20 boys)	3.03 (13 girls) 6.88 (7 boys)	1.50 (n = 3)

20,22D/StAR = 20, 22-desmolase/steroidogenic acute regulatory protein deficiency; 21-OHDSW = 21-hydroxylase deficiency, salt-wasting type; 21-OHDSV = 21-hydroxylase deficiency, simple virilizing type; 3β-HSD = 3β-hydroxysteroid dehydrogenase deficiency; SDS = standard deviation score
* $p<0.001$

one girl (100%) with 3β-HSD deficiency (clitoromegaly and labial fusion). The age at initial presentation of the 21-OHDSW patients with genital ambiguity was slightly younger than those with normal male genitalia, but the difference was without statistical significance (0.12 and 0.17 years, respectively, $p = 0.60$). Scrotal-like labia were present in 10 of 19 girls (52.6%) with 21-OHDSW, but in none of the 13 girls with 21-OHDSV. Pubic hair was noted in eight of 13 girls (61.5%) and four of seven boys (57.1%) with 21-OHDSV. The median phallus lengths were 2.63 and 3.87 cm in girls and boys with 21-OHDSW, respectively, and 3.03 cm and 6.88 cm in girls and boys with 21-OHDSV, respectively. Three patients with 3β-HSD deficiency had a small phallus with a median length of 1.50 cm.

The results of laboratory investigations in patients in each type of congenital adrenal hyperplasia are shown in Table 2. The median basal cortisol levels in patients with 21-OHDSW and 21-OHDSV were significantly greater than those with 20,22D/StAR deficiency and 3β-HSD deficiency ($p<0.001$). The median stimulated cortisol level after a 250-microgram ACTH was given to patients with 21-OHDSV was 19.49 μg/dL, which was above the 18 μg/dL cut-point for diagnosis of adrenal insufficiency. The median basal 17-OHP levels were markedly elevated in 21-OHDSW and 21-OHDSV patients (20,264 and 5,985 ng/dL, respectively), and was significantly greater in patients with 21-OHDSW than in those with 21-OHDSV ($p<0.001$). The basal and stimulated 17-OHP levels were very low in patients with 20,22D/StAR deficiency. The median testosterone level was significantly greater level in patients with 21-OHDSW than in those with 21-OHDSV. An MRI/CT abdominal scan in all cases with 20,22D/StAR and 3β-HSD deficiencies revealed bilateral adrenal enlargement two to three times normal size for ages. An MRI of the adrenal glands was performed in a patient who had a normal stimulated cortisol level of 24.5 μg/dL and a mildly elevated 17-OHP level of 2,450 ng/dL to exclude an androgen-producing adrenal tumor. The bilateral adrenal enlargement demonstrated by the MRI scan led to the diagnosis of 21-OHDSV in this patient.

All patients with salt-wasting crisis responded well to glucocorticoid and mineralocorticoid treatment and those with 21-OHDSV responded well to

Table 2. Laboratory investigations at initial presentation

	20,22D/StAR (n = 4)	21-OHDSW (n = 39)	21-OHDSV (n = 20)	3β-HSD (n = 3)
Chromosome				
46,XX	2	19/19	9/13	1
46,XY	2	-/20	-/17	2
Na (mmol/L)	114*	120*	137	115*
K (mmol/L)	6.7*	7.6*	4.3	6.0*
Cl (mmol/L)	90*	92*	105	90*
CO_2 (mmol/L)	12.3*	13.5*	23.3	12.7*
Basal cortisol level (μg/dL)	0.82*	9.22	9.50	2.20*
Peak cortisol level after ACTH test (μg/dL)	8.28*	11.06*	19.49	5.68*
Basal 17-OHP level (ng/dL)	260*	20,264 (n = 24)	5,985* (n = 14)	ND
Peak 17-OHP level (ng/dL)	340*	23,914 (n = 24)	24,886 (n = 14)	ND
Testosterone (ng/mL)	0.02*	6.55	2.16*	0.44*

20,22D/StAR = 20, 22-desmolase/steroidogenic acute regulatory protein deficiency; 21-OHDSW = 21-hydroxylase deficiency, salt-wasting type; 21-OHDSV = 21-hydroxylase deficiency, simple virilizing type; 3β-HSD = 3β-hydroxysteroid dehydrogenase deficiency; ACTH = adrenocorticotropin hormone; ND = not done
* $p<0.001$

glucocorticoid therapy. All of the presented female patients with ambiguous genitalia underwent a clitoroplasty at the age of one to three years, at the convenience of the parents. For monitoring of the patient's compliance and adjustment of the dosage of glucocorticoid, the 17-OHP level was measured every 4-6 months in patients with 21-OH deficiency and the ACTH level measured in patients with 20,22D/StAR and 3β-HSD deficiencies. All patients except one were assigned correctly as a boy or a girl at the initial presentation. The one exception was a girl with 21-OHDSW who was initially gender assigned as a boy due to marked clitoromegaly of 2.5 cm with fusion of the urogenital slit and scrotal-like labia. The parents decided to have the baby's gender reassigned as female, and the girl underwent clitoroplasty and genitoplasty at the age of one year. Two phenotypic female patients with 20,22D/StAR deficiency who had XY chromosomes, each underwent an orchidectomy at the age of three years, after which they were raised as normal girls.

Discussion

The results of the present study were consistent with studies from Western countries, with the majority of the presented CAH patients being 21-OHDSW type, presenting in the neonatal period, and the 21-OHDSV type presenting in the childhood period, with a few cases of 20,22D/StAR and 3β-HSD deficiencies. There were no statistical differences in ages at initial presentation between normal female, normal male, or ambiguous genitalia. The median basal and stimulated cortisol levels in patients with 20,22D/StAR and 3β-HSD CAH were extremely low despite the salt wasting crisis in these patients, which represented the severe enzymatic defect of cortisol production in severe stress. The median cortisol level in patients with 21-OHDSW, elevated at basal condition and slightly increased after the ACTH stimulation test, could be explained by the maximal response of the adrenals to severe stress at the initial presentation. In patients with 21-OHDSV, a condition partially involving an enzymatic defect in cortisol production, the median stimulated cortisol levels were markedly increased over the cut-point criteria for diagnosis of adrenal insufficiency.

In the present study, the median basal 17-OHP level in patients with 21-OHDSW was markedly elevated and increased only slightly when stimulated, but which represented the maximal response of the adrenals in this critical condition. The basal 17-OHP level in patients with 21-OHDSV was significantly lower than in those with 21-OHDSW, but was markedly over the cut-point level for diagnosis of 21-OH deficiency and was markedly elevated at four times the baseline level after being stimulated by a 250-microgram ACTH. Besides the 17-OHP level, the chromosomal studies and MRIs of the adrenal glands

were helpful in differentiating each type of CAH, particularly the salt-wasting patients who were female with an XY chromosome, which can lead to the diagnosis of 20,22D/StAR deficiency. This type of CAH was earlier described in the first reported case in Thailand from Department of Pediatrics, Faculty of Medicine, Prince of Songkla University[13].

The incidences of both 20,22D/StAR and 3β-HSD CAH are extremely rare, with together accounting for <5% of all CAH cases. In the present study, four patients (6.1%) were diagnosed with 20,22D/StAR and three patients (4.5%) with 3β-HSD CAH. Two of our female phenotype patients with severe salt-wasting had an XY chromosome, which led to the definite diagnosis of 20,22D/StAR CAH. Two of our female phenotype patients with severe salt-wasting had an XX chromosome, which made it difficult to differentiate between 20,22D/StAR CAH and congenital adrenal hypoplasia. In this situation, an MRI of the adrenals was helpful for definite diagnosis. The bilateral enlarged adrenals suggested the diagnosis of 20,22D/StAR CAH and small adrenals suggested the diagnosis of congenital adrenal hypoplasia. The clinical characteristics of skin hyperpigmentation and a low aldosterone level in salt-wasting patients are helpful to exclude hypoaldosteronism and pseudohypoaldosteronism as described in the first reported case in Thailand from Department of Pediatrics, Faculty of Medicine, Prince of Songkla University[14]. In 3β-HSD CAH, genital ambiguity is present in patients with either the XX or XY sex chromosome. In this condition, the clinical features of salt-wasting crisis, with low testosterone (in XY patients) level and the bilateral enlarged adrenal glands revealed by an MRI are helpful in the diagnosis of 3β-HSD CAH.

The authors found no patients with 11-OH or 17-OH deficiency in the present study, which was not entirely unusual in that these are quite rare types of CAH, usually asymptomatic, or minimal clinical features, no genital ambiguity and no salt wasting, and presenting at a later age concerned with delayed puberty.

Despite the genital ambiguity of the presented patients, all except one were assigned correctly as a boy or a girl at the initial presentation. The exception was one patient suffering at presentation from severe salt wasting who had male-like genitalia with a 2.5 cm phallus and was thus thought to be male. After the diagnosis was made and the proper treatment was provided, the parents decided to have the infant undergo surgical correction and had the gender reassigned as female.

There were a few limitations to the present study. Firstly, the present study was based on hospital-based patients, most of them were referred, as our institute is the tertiary care hospital in southern Thailand. Thus, it is possible that patients with mild clinical features would not be referred, or on the other hand, some severe cases particularly those without ambiguous genitalia, might not be diagnosed at all and, with severe conditions, could die without definite diagnosis. Secondly, genetic molecular studies, a gold standard to confirm the definite diagnosis of 21-OHD congenital adrenal hyperplasia, were not available at the time of the present study. The authors expect that these limitations will be solved in the future.

In conclusion, a 20-year review of CAH in our referral institute in southern Thailand found the most common type of CAH to be 21-hydroxylase deficiency. The most common clinical manifestation in the newborn period was dehydration, and in the childhood period an enlarged clitoris/penis. The present study also indicates that the most useful investigation for definite diagnosis of 21-hydroxylase deficiency is basal 17-OHP level: a markedly elevated level suggests 21-OH deficiency CAH while an undetectable or a low level in phenotypic female infant suggests 20,22D/StAR CAH.

Potential conflicts of interest

None.

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การวินิจฉัยและการรักษาโรคเปลือกต่อมหมวกไตหนาแต่กำเนิด: ประสบการณ์ 20 ปี ในโรงพยาบาลสงขลานครินทร์

สมจิตร์ จารุรัตนศิริกุล, เทอดพงษ์ ทองศรีราช

วัตถุประสงค์: *เพื่อศึกษาชนิดของโรคเปลือกต่อมหมวกไตหนาแต่กำเนิด ลักษณะทางคลินิกและผลการตรวจทางห้องปฏิบัติการในโรคเปลือกต่อมหมวกไตหนาแต่กำเนิดแต่ละชนิด*

วัสดุและวิธีการ: *การศึกษาย้อนหลังจากเวชระเบียนของผู้ป่วยเด็กที่ได้รับการวินิจฉัยโรคเปลือกต่อมหมวกไตหนาแต่กำเนิด*

ผลการศึกษา: *ในช่วงระยะเวลา 20 ปี (พ.ศ. 2534-2554) มีผู้ป่วยเด็กที่ได้รับการวินิจฉัยโรคเปลือกต่อมหมวกไตหนาแต่กำเนิด จำนวน 66 ราย ชนิดที่พบมากที่สุดคือ salt-wasting 21-hydroxylase deficiency (21-OHDSW) (ร้อยละ 59.1) รองลงมาคือ simple virilizing 21-hydroxylase deficiency (21-OHDSV) (ร้อยละ 30.3) และพบ 20, 22-desmolase/steroidogenic acute regulatory protein (20,22D/StAR) deficiency (ร้อยละ 6.1) and 3β-hydroxysteroid dehydrogenase (3β-HSD) deficiency (ร้อยละ 4.5) ระดับของ cortisol หลังการกระตุ้นมีค่าน้อยกว่า 18 มคก./ดล. ในผู้ป่วยส่วนใหญ่ และมีผู้ป่วย 20 รายที่เป็น 21-OHDSV มีค่ามัธยฐานของ cortisol 19.49 มคก./ดล. มัธยฐานของค่าเริ่มต้นของ 17-hydroxyprogesterone (17-OHP) มีระดับสูงมากในผู้ป่วย 21-OHDSW และ 21-OHDSV (20,264 และ 5,985 นก./ดล. ตามลำดับ) แต่มีระดับต่ำในผู้ป่วย 20,22D/StAR deficiency (260 นก./ดล.) การตรวจทางรังสีวิทยาที่พบเปลือกต่อมหมวกไตหนาทั้งสองข้างช่วยในการวินิจฉัยชนิด 20,22D/StAR และ 3β-HSD deficiency*

สรุป: *ชนิดของโรคเปลือกต่อมหมวกไตหนาแต่กำเนิดที่พบบ่อยที่สุดคือ 21-hydroxylase deficiency การตรวจทางห้องปฏิบัติการเบื้องต้น (cortisol, 17-OHP, testosterone) ช่วยในการแยกชนิดของโรคเปลือกต่อมหมวกไตหนาแต่กำเนิด ระดับ 17-OHP และ cortisol ที่ต่ำในทารกเพศหญิงที่มีภาวะ salt-wasting ช่วยในการวินิจฉัยโรค CAH ชนิด 20,22D/StAR deficiency*