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CONGENITAL ADRENAL HYPERPLASIA IN MALAYSIAN PAEDIATRIC ENDOCRINE TERTIARY CENTRE: A REVIEW OF CASES AND GROWTH OUTCOME

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CONGENITAL ADRENAL HYPERPLASIA IN MALAYSIAN PAEDIATRIC ENDOCRINE TERTIARY CENTRE: A REVIEW OF CASES AND GROWTH OUTCOME

ABSTRACT

Introduction: Congenital adrenal hyperplasia(CAH) is a group of autosomal recessive disorder resulting in abnormality of cortisol, aldosterone and/or testosterone synthesis. The worldwide incidence is between 1:10000-20000. There are limited data on CAH children in Malaysia. We aim to describe the clinical phenotypes of CAH and growth outcome among children with CAH as well as other associated related complications.

Methods: We reviewed 38 eligible patients' notes seen between 1982-2016. CAH was classified as classical [salt wasting(SW) or simple virilizing(SV)] or non-classical(NCCAH). Enzyme diagnosis was made following clinical presentation of AG and SW with supportive biochemical parameters. This is confirmed with raised 17OHP and testosterone level. Auxology, biochemical parameters and dose of glucocorticoids were reviewed at 5 different time points; 2 years, 5 years, 10 years, 15 years and at final height.

Results: All of our patients were diagnosed as Classical CAH. SW is the most common type of CAH with 60.5%(n=23), 26.3% (n=10) in SV and transient CAH 13.2%(n=5). 21-OHD is the most common enzyme diagnosis of 92%(n=35). Two of patient had confirmed diagnosis of 3β-OHD and one patient presumed to have 11-β OHD. Mean age of presentation was at 0.76±1.5 years. Majority presented within the first 6 months of life: 78.9%(n=30). Majority 60.5%(n=23) were females. There were 39.5%(n=15) Malays, 33.3%(n=10) Chinese and 16.7%(n=5) Indians. Three cases of parental consanguinity reported. 31.6%(n=12) presented with salt wasting crisis. Ten of our patient had received

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treatment with cortisone acetate before changing to hydrocortisone once it available in Malaysia after 1996. The height SDS were observed to be lower at final height with -1.63±1.7 in male and -1.29±1.5 in female. However, children with CAH in UMMC achieved acceptable adult height comparable to Malaysian populations standard (male: -1.69 and female: -1.54 SDS). Those with poorer control disease were shorter with lower SDS compared to those with good disease control although statistically not significant. Children who were exposed to cortisone were shorter at final height compared those on only hydrocortisone. However, due to small study number it was not significant statistically (p-value 0.312). Fifteen children (46.5%) developed precocious puberty(PP) with mean age of 7.68 ± 2.5 years among male (n=9) and female (n=6) at 7.03 ± 1.2 years. Out of this 12 had central precocious puberty(CPP) and 3 developed peripheral precocious puberty(PPP). Only one patient developed testicular adrenal rest tumour (3%). One third of our patient were obese. No difference seen between mean dose glucocorticoids among obese and non- obese.

Conclusion: 1 out of 5 children with CAH presented after 1 year of age. Clitoromegaly can be missed at birth. Older children with virilization need to be investigated for SV-CAH and NC-CAH. Investigations for precocious puberty is required when these children present with sudden growth spurt as early as 5 years old. Screening to look for testicular adrenal rest tumourr need to be done routinely. Inadequate evidence to show higher glucocorticoids leads to obesity in children with CAH.

Keywords: CAH, final height, precocious puberty, TART and obesity

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LIST OF SYMBOLS AND ABBREVIATIONS

CAH	:	Congenital adrenal Hyperplasia
UMMC	:	University Malaya Medical Center
17-OHP	:	17 Hydroxyprogesterone
T	:	Testosterone
DHEAS	:	Dehydroepiandrosterone
ACTH	:	Adrenocorticotrophic Hormone
CRH	:	Corticotropin-releasing hormone
BMI	:	Body Mass Index
TART	:	Testicular Adrenal Rest Tumour
OART	:	Ovarian Adrenal Rest Tumour
SD	:	Standard deviation
SDS	:	Standard deviation score
MPH	:	Mid- parental height
WHO	:	World Health Organization
CDC	:	Centre for disease control and prevention
3β-OH	:	3β- Hydroxysteroid dehydrogenase
11β-OH	:	11β- Hydroxylase
21-OHD	:	21- Hydroxylase
GC	:	Glucocorticoid
MC	:	Mineralocorticoid
HCT	:	Hydrocortisone
PP	:	Precocious Puberty

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CHAPTER 1: INTRODUCTION

1.1: Basic Anatomy and physiology:

Adrenal gland is an endocrine organ that plays an important role in producing adrenocortical hormones. It is located at superior pole of both kidneys and composed of an outer cortex and inner medulla surrounded by outer capsule (Fig 1.1). The cortex has three histologically distinct zones namely zona glomerulosa, zona fasciculata and zona reticularis. Adrenal steroids are synthesized in the cortex from cholesterol in series of enzymatic steps. Three main hormones are produced in the three different zones in the adrenal cortex serving different types of function and give different types of effect. (1)

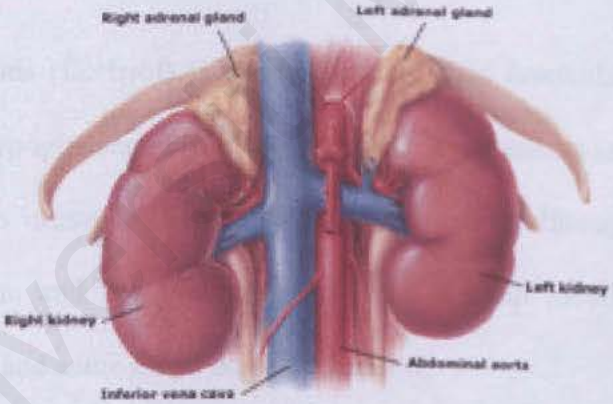

Figure 1.1: Location of adrenal glands; adapted from Up to Date

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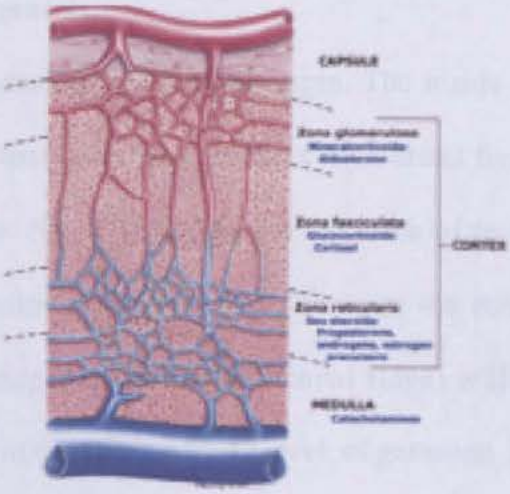

Figure 1.2: Layers of adrenal glands; adapted from Up to Date

Minerolocorticoid (aldosterone) is synthesized in zona glomerulosa. Its main role is to retain sodium and excrete potassium at kidney level in response to hypovolemia, or hypotension to help to increase systemic blood pressure.

Glucocorticoids (Cortisol) is synthesized in zona fasciculata. It is released in response to stress, hypoglycaemia (low blood sugar), hypotension and in any emergency situation. It helps to improve/increase blood glucose level through gluconeogenesis, catabolic metabolism, and has function in fat and protein metabolism. It has anti-inflammatory action and some effect on salt retention.

Androgen namely testosterone is synthesized in zona reticularis. Testosterone is important for sex hormones production; and through aromatisation produces oestrogen. (Fig 1.2)

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1.2 Fetal Adrenals Steroidogenesis:

The adrenal gland has a dual embryological origin. The inside core of adrenal medulla arises from neural crest tissue whereas adrenal cortex arises from the coelomic mesoderm of the urogenital ridge. (Fig.1.3) During the 5th week of fetal development, mesothelial cells from the posterior abdominal wall, between the root of the bowel mesentery and developing mesonephros/ gonad (urogenital ridge) will proliferate and form the fetal or primitive cortex of the adrenal by 5th week of gestation. It then followed by development of primitive cortex (later forms the adult or definitive cortex) at 6th week gestation. By 8 weeks of gestation, the fetus acquires a rudimentary but distinct adrenal cortex, consists of 3 zones namely (2, 3):

1. Fetal zone: dominates at mid-gestation (16–20 weeks), exhibit steroid-secreting cells
2. Definitive zone: zona glomerulosa. After 22-24 weeks expresses enzymes that suggest mineralocorticoid synthesis
3. Transitional zone: zona fasciculata that later after 25-30 weeks expresses enzymes that suggest glucocorticoid synthesis

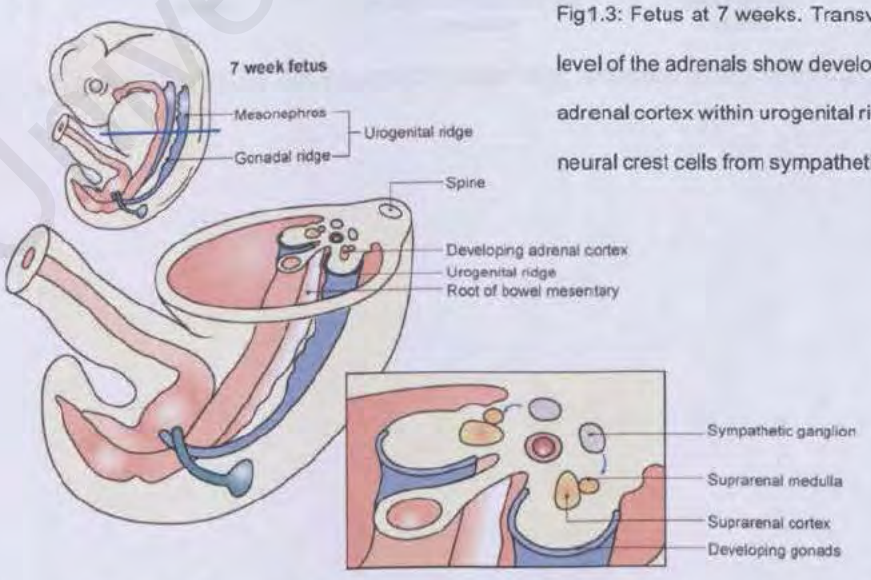

Fig1.3: Fetus at 7 weeks. Transverse sections at level of the adrenals show developing gonads and adrenal cortex within urogenital ridge. Migration of neural crest cells from sympathetic ganglion forms

Figure 1.3: Fetal Adrenal Development; adapted from Barwick, 2005

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Throughout the fetal period, its adrenal cortex comprised of two distinct zones: the outer definitive zone and large inner fetal zone (Fig.1.4). The transitional zone comprises the outer edge of fetal zone and forms a functionally distinct compartment in between. Fetal adrenal cortical growth involves several cellular processes: hypertrophy, hyperplasia, apoptosis, and migration. Subsequently by late gestation, the fetal adrenal cortex resembles a rudimentary form of the adult adrenal cortex. Soon after birth, the primate adrenal cortex dramatically remodels during the first 6 weeks of postnatal life (apoptosis) resulting to atrophy of fetal zone and development of the zone glomerulosa and fasciculata. A final layer, the zona reticularis forms after birth at about 3 years age.(2, 3)

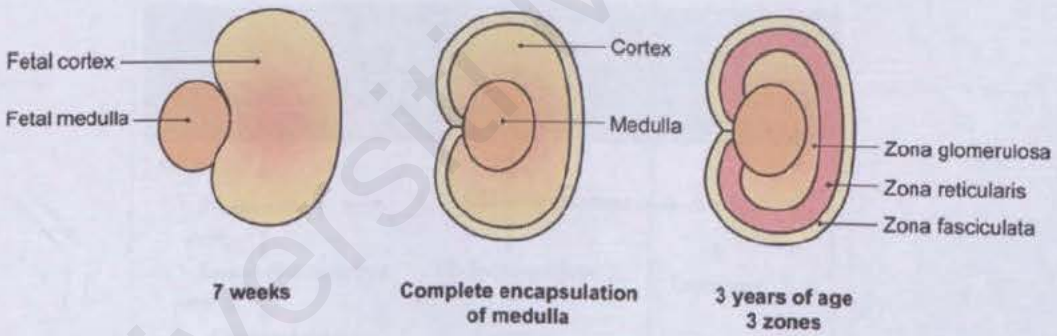

Figure1.4: Fetal adrenal development anatomy; adapted from Barwick, 2005

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In late-gestation, fetal androgen and oestrogen are majorly derived from placenta. The placenta lacks cytochrome P450 (CYP17) and 17α-hydroxylase and 17,20-lyase activities. Placenta synthesizes oestrogen from precursors received from the fetal adrenal cortex. The adult zone or definitive zone of the fetal adrenal cortex lacks the 3β-hydroxysteroid dehydrogenase enzyme (Fig.1.e) hence cannot synthesize progesterone or 17α-hydroxyprogesterone. Whereas following response to ACTH, fetal zone of the fetal adrenal cortex continues to secrete dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) in larger quantity. The other steroidogenic enzymes appear to be present, thus does produce some cortisol and aldosterone (either from cholesterol via the small amount of 3b-HSD). These steroidogenic intermediates used in biosynthesis of estrogens by placenta, bypassing CYP17 (Fig.1.5).(4)

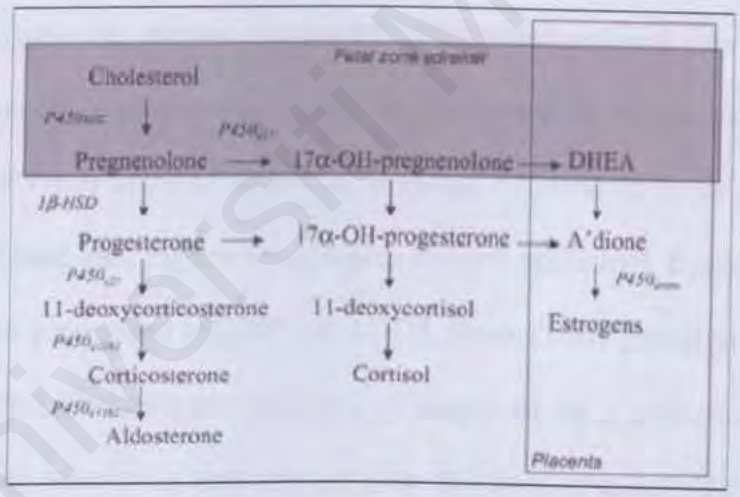

Fig.1.5: Steroid biosynthesis in the developing primate fetus. The fetal zone of the fetal adrenal cortex is capable of performing the reactions in the shaded area. The overlapping box (right) represents estrogen biosynthesis by the placenta. A-dione, androstenedione

The importance of understanding fetal adrenals is namely because of the surge and fluctuating levels of 17OHP during early infantile period. Hence why in preterm babies and 48 hours after birth, the 17OHP levels can be high. 17OHP levels to rule out CAH must be taken after D3 of life to allow natural involution of fetal zone.

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1.3 The Hypothalamo- Pituitary- Adrenal axis:

1.3.1 Regulation of Cortisol secretion

In response to Corticotropin releasing hormone (CRH) released from the hypothalamus, anterior pituitary will be stimulated to synthesize and release of adrenocorticotropic hormone (ACTH). ACTH is synthesized as part of large molecular weight precursor peptide known as pro-opiomelanocortin (POMC). These POMC will undergoes series of proteolytic cleavages, yielding several biologically active peptides. The N-terminal glycopeptide (POMC 1-75) involves with steroidogenesis. At short term (min to hours), ACTH effects stimulates steroidogenesis at the adrenal gland by interacting with receptors that stimulate the production of cAMP. ACTH, acting via cAMP stimulates the biosynthesis of LDL receptors and the uptake of LDL, which provides most of the cholesterol used for steroidogenesis. At long term (hour to days), ACTH effects cause the increase uptake of LDL cholesterol and expression of genes encoding enzyme for cortisol secretion; the principal steroidal product of human adrenal. Cortisol and ACTH is secreted following response to physical stress (major surgery, severe trauma, blood loss, high fever, illnesses and inflammation). Cortisol has negative feedback towards production of CRH and ACTH. During early period, it inhibits release of ACTH and CRH from secretory granules. At long term, the glucocorticoids directly at steroidogenesis by inhibits the transcription gene of POMC (Fig 1.6) (1)

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1.3.2 Regulation of Aldosterone Secretion

Mineralocorticoid (Aldosterone) secretion is mainly regulated by the renin-angiotensin system and potassium levels, with ACTH only having at short term effect. Following decrease of intravascular volume and blood pressure, sodium depletion, upright posture and vasodilatory drugs, renin will be secreted at juxtaglomerular apparatus of kidney. Renin cleaves angiotensinogen to angiotensin I and later converted to angiotensin II by angiotensin- converting enzyme (ACE) from the lungs and other tissues. Angiotensin II is a potent stimulator of aldosterone secretion as well as stimulates arteriolar vasoconstriction to increase blood pressure. (1)

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1.3.3 Regulation of Adrenal Androgens.

Adrenal androgens namely DHEA, DHEAS and androstenedione are secreted by the zona reticularis at adrenal cortex. These andrenal androgens will be converted at peripheral to testosterone. Large amounts of DHEA and DHEAS are secreted from fetal adrenal. However, as the fetal zone involutes after birth the concentration fall rapidly until the onset of adrenarche, usually around age 7-8 years. ACTH plays role in stimulating production of adrenal androgens. Other factor implicated in stimulation of androgens include decrease in expression of 3β-hydroxysteroid dehydrogenase in zona glomerularis. (1)

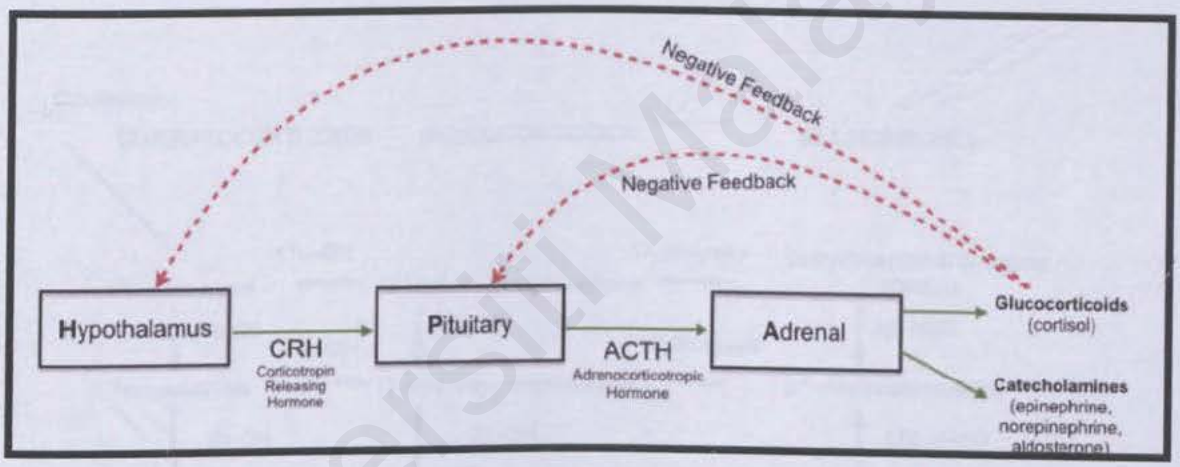

Fig 1.6: Hypothalamus- Pituitary- Adrenal Axis

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1.4 Adrenal Steroidogenesis

Adrenal corticosteroid hormones biosynthesis involves steroidogenic enzymes of cytochrome P450 are under regulation of pituitary gland. The pituitary regulates adrenal steroidogenesis via adrenocorticotropic hormone (ACTH) stimulates steroid synthesis by acting on the adrenals to increase the conversion of cholesterol to pregnenolone, the principal substrate for the steroidogenic pathways. The central nervous system controls the secretion of ACTH, its diurnal variation, and its increase hypothalamic-pituitary-adrenal feedback system is mediated through the circulating level of plasma cortisol; any condition that decreases cortisol secretion results in increased ACTH secretion. Cortisol therefore exerts a negative feedback effect on ACTH secretion. (Fig.1.7) (1)

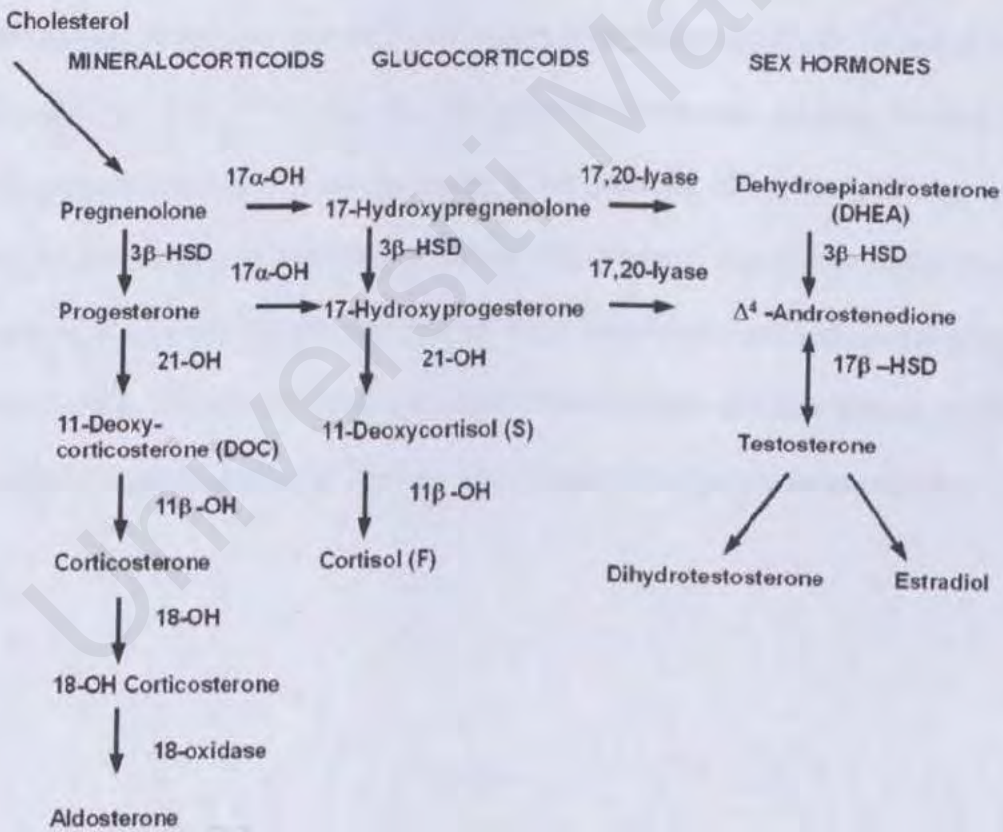

Figure 1.7 : Adrenal Steroidogenesis

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In cases due to defect of one of enzyme that blocks the cortisol synthesis, It will cause impairment in cortisol-mediated negative feedback control of ACTH secretion. These will result to over-secretion of ACTH. Subsequently, it will stimulate excessive synthesis of the adrenal products of those pathways unimpaired by an enzyme deficiency (adrenal androgens) and causes an accumulation of precursor molecules in pathways blocked by an enzyme deficiency namely congenital adrenal hyperplasia.

Congenital adrenal hyperplasia (CAH) is a rare inherited disorders of adrenal steroidogenesis consists of group of autosomal recessive disorder. This resulted to impairment of cortisol synthesis which resulted to spectrum of clinical presentation and sequelae resulted from the treatment and clinical condition. To date, limited data available as per incidence and outcomes of CAH among Malaysian population. As one of the main endocrinology tertiary referral for the country, University Malaya Medical Center received numbers referral and managing CAH patients. However, minimal is known about the outcomes of these patients. Hence, it is foremost importance for the study to be done to analyse on our CAH patients; types and clinical outcomes and clinical progression of the disease. It would be helpful for future management of CAH disease whether any association found in particular the height outcomes with the treatment received.

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2.1 Overview of CAH

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders which resulted to impairment of cortisol synthesis. This is mainly due to defects in cortisol biosynthesis secondary to deficiencies in one of the enzymatic steps (5). Cortisol deficiency resulted to excessive secretion of CRH and ACTH hence causing hyperplasia of adrenal glands. Regardless of either 21- hydroxylase, 11β- hydroxylase or 3β-hydroxysteroid dehydrogenase deficiency, excessive trophic hormones stimulation resulted to excessive sex hormones precursor production. The end products of these includes androgens and some to oestrogen. (6). The sequalae resulted to virilization of affected females in utero due to hyperandrogenism. However, it will cause undervirilze males whom being affected by 3β-hydoxylase or 17α- hyroxylase deficiency due to insufficient quantities of androgen. Those whom have steroidogenic defects will also have disruption with aldosterone synthesis; hence inability to maintain normal sodium balance. It may cause severe hyponatremic dehydration, shock and death if left untreated. (6-8)

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2.2 Spectrum of Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia is a rare disorders with spectrum of phenotype depending on the enzyme deficiency involves. It includes either 21- Hydroxylase deficiency (21-OH), 3β- Hydroxysteroid dehydrogenase (3β-OH), 11β- Hydroxylase (11β-OH), 17α- hydroxylase deficiency or rarely lipoid hyperplasia (Fig.2-1).

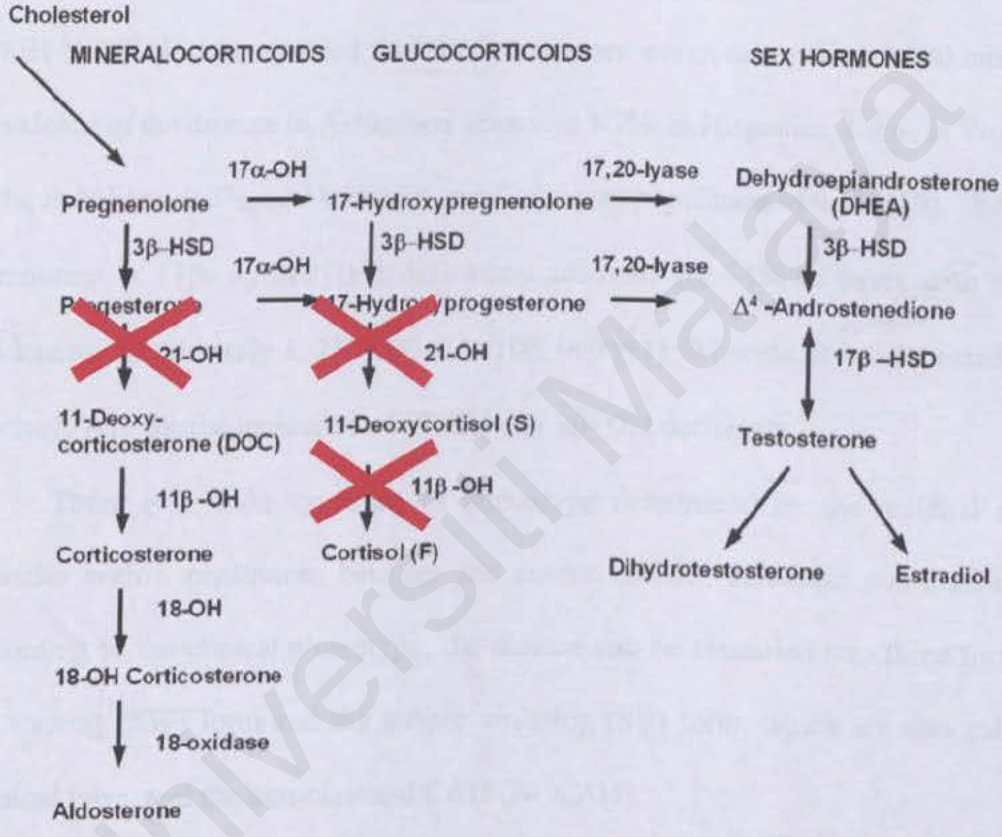

Fig 2.1 – Step involves in Adrenal Steroidogenesis

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2.3 Prevalence of CAH

21- Hydroxylase (21-OH) deficiency accounts approximately 95% of the cases followed by 11β- hydroxylase deficiency of 5% and 1% for 3β- hydroxysteroid dehydrogenase and 17α- hydroxylase deficiency. Pang et all reported that classical 21-OH deficiency occurred with incidence of 1: 10 000 – 1: 20 000 births. Higher rates of classic CAH have been reported among Yupic Eskimos of Alaska (1: 280) as well as the French island of La Réunion with incidence of 1:2,100 (9). Comparatively, incidence of 21-OH NC-CAH was reported far more commoner which occurs in 1/8,000 births. The prevalence of the disease in Ashkenazi Jews was 3.7%; in Hispanics, 1.9%; in Yugoslavs, 1.6%; in Italians, 0.3%; and in the diverse Caucasian population of 0.1% (10). The second commonest is 11β- hydroxylase deficiency accounts for ~5% of cases with reported incidence approximately 1: 250,000 to 1: 100, 000 (11). Whereas, it was reported as 1%; relatively rare for the incidence of 17-OH and 3β- OH deficiency.

There is a wide spectrum of phenotype determined by the residual enzyme activities with a continuum between the severe classic and mild non-classic form. According to the clinical phenotype, the disease can be classified into three forms, the salt wasting (SW) form and the simple virilising (SV) form, which are also called the classical form, and the non-classical CAH (NCCAH).

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2.4 Incidence of Congenital Adrenal Hyperplasia in Asia

To date there are limited data on CAH in Malaysian population. Collaboration among the local endocrine centre of Putrajaya and Universiti Putra Malaysia unable to estimate the prevalence of CAH in Malaysia due to limitation of study being conducted in a single tertiary centre and small sample size (12). Thailand has had performed its first newborn screening program of CAH in year 2009 and reported high incidence of 1:19,521 (13). In year 2015, Japanese has reported the finding following their mass newborn CAH screening program in Tokyo prefecture. The incidence was reported as high as 1/19,859.

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2.5 Clinical Presentation of CAH

CAH patients presented with range of severity due to a combination of the disease-related glucocorticoid deficiencies resulted to accumulation of androgen excess. The salt wasting (SW) form of CAH is characterized by a life-threatening metabolic crisis, typically presenting in the first weeks after birth, with salt-loss, hyponatremia, hyperkalemia, dehydration, shock; commonly brought to medical attention amongst boy. Whereas in girls, CAH usually detected within few days of life due to ambiguous genitalia as reported by Khalid eta al. (5, 14, 15). Whereas, the simple virilising (SV) form is usually recognized by a variable degree of clitoris hypertrophy, posterior labial fusion in females and pseudoprecocious puberty in males (14). One of three clinical features usually precipitated investigation and diagnosis: virilisation of the female genitalia, premature pubarche or salt-wasting crises. Genital virilisation was present in over three-quarters of girls and salt-wasting crises were reported in a quarter of all children. Overlapping presentation of salt wasting and virilization also observed among study done (Table 2.1).

Table 2.1: Reason for Clinical Presentation CAH : Khalid et al (onset before 30 days) and Larsson et al (onset before 60 months)

Authors	Reason for Clinical Presentation	Total (%)	Boys N	Girls N
Khalid et al (2014) Great Britain	**Salt Wasting**	27 **(35%)**	15	3
	Virilizing of female genitalia	34 **(44%)**	-	34
	Incomplete masculinization	2 (2.6%)	-	2
	Adrenal insufficiency	3 (3.8%)	2	1
	Affected sibling	11 (14.2%)	5	6
Larsson et al (1990) Sweden	**Salt Wasting** only	47 **(32.9%)**	47	-
	SW + Virilizing	45 (31.4%)	-	45
	SW + AG	1 (0.7%)	1	-
	Simple Virilizing	50 **(34.9%)**	15	35
	Affected sibling	2 (1.4%)	1	1

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The non-classical form is rarely diagnosed before the onset of puberty. Those patient with NC-CAH does not have not have cortisol deficiency, but instead have manifestations of hyperandrogenism hence later presentation in childhood or in early adulthood. These patients can present with early pubarche (5-10%)(16), or as young women with hirsutism (60%), oligomenorrhoea or amenorrhoea (54%) with polycystic ovaries, and acne (33%) whereas in male may remain asymptomatic (17) (18).

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2.6 Investigation and Diagnosis of CAH

In those presented with ambiguous genitalia, it is at upmost important to exclude diagnosis of CAH. A good history and physical examination is crucial to confirm diagnosis of CAH or other differential diagnoses under umbrella of disorders of sex development. Key investigations crucial to be done are (19) :

2.6.1 Key initial investigations in child with ambiguous genitalia

- Day 1 - Karyotyping with rapid FISH to determine the genetic make-up as well as determine SRYgene
- 48- 72 hours of life
    - Chemistry samples : Urea and electrolytes, blood glusose levels, cortisol and ACTH
- Ultrasound scan of abdomen and pelvis : to look on gonads, mullerian structures, adrenal glands and renal structures.

2.6.2 Further investigations (After 48- 72 hours of life)

- Serum testosterone, oestradiol
- 17 hydroxyprogesterone and 11 deoxycortisol – to exclude CAH
- Adrenal androgens : androstenedione, hehydroepiandostenedione sulphates – to look for defects in the cascade of androgens that lead to the production of testosterone.
- Gonadotropins : luteinising hormone (LH), follicle stimulating hormone (FSH). Neonates have a physiological 'mini-puberty', with gonadotropin levels peaking at 4-6 weeks post- delivery.
- Spot Urinary Profile (USP)

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It is recommended to do early morning Serum 17-hydroxyprogesterone (17-OHP) to confirm diagnosis of CAH (20). In a case of classic CAH, a very high concentration of Serum 17-OHP of more than 300 nmo/L taken at any random time after day 3 of life in full term infant is highly suggestive (normal less than 3 nmol/L) (20).

However, in borderline level of Se 17 OHP between 6-300 nmo/L is suggestive of NCCAH and if less than 6 nmol/L can be normal or NCCAH. Hence, gold standard of cosyntropin stimulation test is recommended to make up complete adrenocorticotropin profile following stimulation. However, the test was not feasible to most country hence short synacthen test is useful in cases suspected CAH (19). If the level of 17 OHP in between 31-300 nmol/L – NCCAH is more likely (20) and level below 50 nmol/L post stimulation is consider normal/ heterozygote (20) Other steroids whose levels are usually elevated include 21-deoxycortisol, androstenedione, and testosterone (20) Elevated plasma renin activity (PRA) and a reduced ratio of aldosterone to PRA indicate impaired aldosterone synthesis and can differentiate salt wasters from simple virilizers (21) after the newborn period.

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2.7. Guidelines for management

2.7.1 Medical Treatment

2.7.1.1 Classical CAH

Society for Paediatric Endocrinology and The Lawson Wilkins Paediatric Endocrine Society (7, 22, 23) has recommended treatment guideline in managing classical CAH. Glucocorticoids (GC) have been used to suppress excessive ACTH production hence reverses adrenal hyperplasia and reduces the level of hormone excess. Hydrocortisone (HC) remains as standard therapy for growing child knowing its short half-life minimizes the adverse side effects of more potent longer-acting GCs, especially growth suppression. The standard dose use is 10-20 mg/m^2 /day. However, oral HC suspension use and long- acting potent GC are strongly not recommended in growing children. At or near completion of linear growth, long-acting GCs may be used (see Table 2), although HC remains a treatment option.

Mineralocorticoid as example fludrocortisone should be use in at diagnosis in classical CAH. (22, 23). Dose in infancy range from 0.05 to 0.30 mg/ day, while typical maintenance doses are 0.05–0.2 mg/ day, depending on the sodium intake. It will help in reducing the vasopressin and ACTH as well as lower the dosage of glucocorticoid required. The need to continue mineralocorticoid based on PRA and blood pressure. Sodium chloride supplements are often needed in infancy at 1–3 g/day in different feedings. (Table 2.2).

Table 2.2 : Maintainance therapy in growing CAH

Drugs	Total Dose	Daily Distribution
GCs : HC	10-15mg/m^2/day	3 times/day
MCs : Fludrocortisone	0.05- 0.2 mg/m^2/day	1-2 times/ day
Sodium Chloride supplementation	1-2 g/day	Divided in several feeding

*GCs- Glucocorticoids, HC- Hydrocortisone, MCs- Mineralocorticoids

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2.7.1.2 Non Classical CAH

For those whom are asymptomatic, the current recommendation does not required them to receive the glucocorticoid treatment. Judicious decision on treatment depending on the advancement of skeletal maturation which predicted to negatively impact their adult height for NCCAH as well as to reduce the hyperandrogenism (22).

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2.7.2 Surgical Intervention

American Academy of Paediatric and ESPE has suggested that for severely virilized (Prader stage $\geq$ 3), females clitoral and perineal reconstruction should be considered in infancy. These will prevent potential side effects and complications from the connection between the urinary tract and peritoneum via Fallopian tubes due to beneficial effects of oestrogen on tissue in early infancy.(24) (25, 26) The feminizing surgery as well as reconstructive surgery for male with hypospadias and orchidopexy; the timing for elective surgery is strongly suggested to be performed during infancy at 6 to 15 months age.(7, 22, 24) It should be performed by an experienced surgeon in a center with multidisciplinary team involves experienced pediatric endocrinologists, mental health professionals, and social work services. Early surgical interventiion can prevent emotional disturbance and trauma that is often observed post operatively should it be done in later age. However still limited data on the long-term outcome of early surgery among the CAH patients. (22)

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2.8 Complications and outcome of CAH

2.8.1 Final Height

There were heterogenous reports on long term follow up and final height outcome in patients with CAH. Treatment consists of glucocorticoid replacement is necessary to suppress ACTH in order to reduce excessive androgen production by substituting for deficient cortisol synthesis. Intended results can be achieved with narrow therapeutic window. As sequalae of the treatment, should these patients were undertreated, it will exposes the patient to the risk of adrenal crisis and allows increased adrenal androgen production, with consequences of advanced bone age and loss of growth potential. Accelarated skeletal maturation is usually associated with development of central precocious puberty. However, if overtreated it will results in growth retardation, truncal obesity and osteopaenia, through the effects of steroids on growth hormone secretion and bone metabolism (1)

In a multinational study of growth patterns in patients with CAH in Germany, Frisch et al. (27) found a reduced maximum growth velocity during puberty. It is supported by other study done by Manoli et al (28) that the height gain during puberty is one of the most potent predictors of FH, beside the type of CAH, mean hydrocortisone dose in the first 2 years, and the mean BMI-SDS in early childhood and after puberty. Attenuated growth during puberty was reported in a multicenter study of 54 patients with CAH in a multicenter study by Muirhead et al.(29) in 2002. In 1997, from the randomized control study done by Silva et al in Brazil looking on the effect of hydrocortisone comparing dose of 15 and 25 mg/m^2/day has showed that height velocity was significantly reduced in those with 25 mg/m^2/day (30). Stikkelbroeck in 2002 has analysed the growth data from 48 patients with salt wasting 21-hydroxylase deficiency and showed that glucocorticoid treatment has significant negative dose-dependent effects on height to age z score, especially in early infancy and puberty using mean dose of > 15 ±7.1 mg/m^2/day.

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(31). Study from Bonfig et al also found that pubertal growth is significantly reduced in both sexes, resulting in a final height at the lower limit of genetic potential. The positive predictive value for short stature rose from below 30% to 60% when hydrocortisone dose of more than 17 mg/m2/day at puberty (32). Bunraungsak et al in year 2013 also looked on the impact of height amongst their CAH patient. They found that the mean final height was significantly low in both type of CAH (salt wasting and simple virilizing) compared to other previous studies from Europe and North America. This finding may be contributed due to choice of glucorcorticoid is prednisolone rather than hydrocortisone at infancy as their patients can't afford for the later (33). Bonfig et al. showed that treatment with prednisolone in children and adolescents with CAH led to worsen final height than hydrocortisone treatment (Table 2.3) (34) Androgen levels should be used in conjunction with growth velocity measurements is important to optimize GC dosing in persons with 21-OHD CAH especially at the first 2 years and during puberty to give better outcome in these patients.

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Table 2.3: Longitudinal Height Data in Various Study

Authors (Date)	Type		(n)	FH(cm)	Ht-SDS		
					2 yrs (n)	P2 (n)	FH (n)
Manoli et al (2002) Greece	SW	M	4	170·8 ± 5·6	0·45 ± 0·2 (2)	0·2 ±1·21 (3)	- 0·57 ± 0·8 (4)
		F	13	156·7 ± 6	−0·33 ± 0·9 (8)	0·09 ± 1·3 (11)	-0.61 ± 1 (13)
	SV	M	11	166.1 ± 6.1	1·3 ± 1·4 (2)	1·25 ± 1·5 (6)	-1.05 ± 1 (11)
		F	14	151·6 ± 5·4	1·3 ± 1·6 (5)	0·1 ± 0·6 (10)	-1.4 ± 1 (14)
Bonfig et al (2009) Germany	SW	M	22	-	-	0.1 ±1.2	0.9 ±0.8
		F	32	-	-	0.1 ±1.4	0.7 ± 0.8
	SV	M	13	-	-	1.2 ±1.6	1.3 ±1.0
		F	25	-	-	0.5 ± 1.2	0.9 ± 1.0
Bunraungsak (2013) Thailand	SW	M	14	159.6 ± 3.3	0.60 ± 1.6 (9)	1.73 ± 1.9* (8)	−1.88 ± 0.6 (2)
		F	35	147.9 ± 5.3	−0.32 ± 1.6 (26)	0.19 ± 1.8 (22)	−1.88 ± 1.1 (14)
	SV	M	5	164	- (0)	4.4 ±0.5 (4)	-1.06 (1)
		F	4	149.4 ± 6.9	1.65 ± 0.2 (2)	0.19 ± 0.8 (4)	−1.56 ± 1.4 (2)

SW- Salt wasting, SV- Simple virilizing, M- Male, F- Female, P2- puberty initiation

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2.8.2 Precocious Puberty

Precocious puberty is defined as the onset of secondary sexual characteristics before the age of 8 years in girls and nine years in boys. The onset of puberty in both girls and boys with classic CAH occurs at the expected chronological age if they were treated satisfactorily from early life. True precocious puberty may occur in some well-treated children with CAH or initiation of glucocorticoid therapy. It is explained by sudden decrease in sex steroid levels and leading to hypothalamic activation. LHRH analogs may be employed as an adjunct to therapy with hydrocortisone in such children. However, in most untreated or poorly treated adolescent girls and in some adolescent boys, spontaneous true pubertal development does not occur until proper treatment is instituted. Studies has suggested that excess adrenal androgens (aromatized to estrogens) inhibit the pubertal pattern of gonadotropin secretion by the hypothalamic-pituitary axis (8). Soliman et al had found six children with CAH but delayed in initiation of of corticosteroid treatment and/or poor compliance developed central precocious puberty (CPP). These patients were treated with standard-dose hydrocortisone and fludrocortisone. By administering depot leuprorelin (3.75 mg subcutaneously every 28 days) for 2 years or longer, able to arrest manifestation of puberty, slowing in pretreatment growth velocity ([GV] 10.8 -+1.5 v 3.65 ± 0.95 cm/yr), increasing the predicted adult height (PAHT) 147.5 -+7 as well as decreasing the bone age to statural age ratio (1.26 ±0.13 v 1.16 ± 0.09)(35)

Whereas , development of peripheral precocious puberty was mainly described as presenting symptoms especially in untreated CAH rather than sequalae of disease. Peripheral precocious puberty is characterized by low or suppressed gonadotrophin with high sex hormones level. Nonetheless, PPP may progress to CPP following treatment. (1, 8)

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2.8.3 Adrenal Rest Tumour

2.8.3.1 Testicular Adrenal Rest tumour

Testicular adrenal rest tumour (TART) was first reported in year 1940. It is call as such in view of morphological and functional resemblance to adrenocortical tissue. It is benign in nature with typical location is within tete of testes. However, it can result to clinical infertility due to tumour compression onto the seminiferous tubules that may lead to obstructive azoospermia and irreversible damage of the surrounding testicular tissue. TARTs are ACTH dependent; hence it can developed during periods of sustained elevation of plasma ACTH (36). The prevalence were widely varies as it was mainly reported in case series . Some paper has reported that it can happen in early childhood as early as 1.8 years old. (37). Several papers reported from their observation, TARTs are higher in those with poor therapeutic compliance (37, 38). Treatment involves include intensifying dose of glucocorticoid for adequate ACTH suppression though does not always successful as reported by Yu MK et al (39). Screening for TARTs was proposed to be done early by age 8 years old (38) and Aycan et all even suggested it to be done at early childhood and annually in peripubertal period (40) Table 2.4 showed summary of prevalence of TARTs in different countries.

Table 2.4: Prevalence of TARTs in different study

Authors	Location	Year of Publication	No of patients (%)	Mean Dose HCT (mg/m2/day)
Dumic et al	Croatia	2017	15/ 51 (29.4%)	NA
Yu MK et al	Korea	2015	8/13 (61.5%)	21.1
Aycan et al	Turkey	2013	11/60 (18.3%)	NA
Stickelbroeck et al	The Netherlands	2001	16/17 (94.1%)	25.4 ±5.7
Avila et al	USA	1996	8/38 (21%)	NA

*NA- Not available.

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2.8.3.2 Ovarian Adrenal Rest Tumour

Comparative to TARTs, ovarian adrenal rest tumour (OARTs) was described but only as case report. The prevalence is much rarer compares to TARTs. However, should ovarian adrenal rest tumours prent, it could impair ovarian function in CAH females by displacing normal ovarian tissue and producing local steroids, which interfere with normal ovarian function. Stikkelbroeck et al in 2004 could not found any prevalence of ovarian adrenal rest tumour amongst their patient(41). It is recommended to proceed with ultrasonography of gonads amongst those female with uncontrolled disease despite adequate glucocorticoid therapy to look for OARTs. Routine surveillance is not recommended. (41, 42)

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2.8.4 Obesity

Overtime, many study has described association of obesity amongst CAH patients. Finkelstein et al done has done a cohort study involving 244 CAH patients and it has showed that obesity was present in approximately one third of patients across phenotypes. It also associated with elevation of BP among classic CAH patients. Their data support the contribution of glucocorticoid therapy to the development of obesity. Study from Volk et al from Germany also demonstrated fifteen subjects (16.8%; female: 7; male: 8) had a BMI SDS of 2.0, which indicated a significantly greater frequency of obesity among patients with CAH than expected for the normal population (43). However, they could not found any relationship between hydrocortisone dose and age. Higher adrenal androgens were commonly observed among their pediatric obese patients, indication the coexistence of both hyperandrogenism and hypercortisolism in a subgroup of difficult-to-treat children (Table 2.5) (44, 45)

Table 2.5 : Obesity in various study

Authors	Prevalence		n	Age	BMI SDS	HCT dose ($mg/m^2/day$)
Volk et al (2006) Germany	15/89 (16.8%)	M	41	8.49 ± 5.02	1.03 ± 1.31	15.9 ± 5.36
		F	48	9.18 ± 4.40	0.75 ± 1.37	13.9 ± 3.99
Subbarayan et al (2014)	25/ 106 (23.6%)	-	106	9.2 (range 0.4- 20.5 years)	0 98 (1 42)	13.3

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CHAPTER 3: OBJECTIVES

3.1: PRIMARY OBJECTIVES

To describe different phenotypes of Congenital Adrenal Hyperplasia in children seen in University Malaya Medical Center.

3.2: SECONDARY OBJECTIVES

1. To describe growth outcome of the children with CAH at different age period.

2. To describe the complications seen in children with CAH:

   i. Precocious puberty

   ii. Obesity

   iii. Adrenal rest tumour (Testicular adrenal rest tumour, ovarian adrenal rest tumour.

3. To describe disease control with final height.

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CHAPTER 4: METHODOLOGY

4.1 Study Design

This is a retrospective cohort study conducted at University Malaya Medical Centre (UMMC) reviewing all available case notes of patient who are diagnosed and followed up for congenital adrenal hyperplasia from year 1982 to December 2016.

Ethical approval was obtained from our local institution's ethics committee. (Ethics Committee/MECID.NO: 201752-5185) *See Appendix 1.*

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4.2 Study Population

Inclusion Criteria

All children with phenotypical description of Congenital Adrenal Hyperplasia were included into the study.

Exclusion Criteria

1. Those whom were labelled as transient CAH were excluded for analysis of outcome data.
2. Patients who are not followed up for a minimum of 2 years (either transfer of care, lost to follow-up or deceased) will not be included in outcome data but will be included for descriptive demographic data.

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4.3 Study Recruitment

Patient with a diagnosis of congenital adrenal hyperplasia will be identified from an existing paediatric endocrinology UMMC database. The diagnosis and types of CAH was based on both clinical symptoms and signs supported by laboratory hormonal analysis. Throughout the study period, newborn screening for CAH and genotyping test were not available. Eligibility were assessed and all patients who fulfil both inclusion and exclusion criteria will be selected.

A comprehensive retrospective review will then be done on the electronic medical records or physical notes of these patients. Clinical data was collected to a pre-defined data collection sheet. *See appendix 2.*

Patient's demographic data, clinical presentation, growth parameters and pubertal characteristics, blood pressure, hormonal and biochemical profiles and the details of treatment at diagnosis were recorded. For growth parameters, weight, height and body mass index (BMI) were collected individually at different time ages [at diagnosis, 2 years, 5 years, 10 years, 15 years age then at reaching final height (FH)] and the data were expressed as the mean (Mean) and standard deviation score (SDS). Body mass index (BMI) was calculated from weight (kg) divided by height (m2) (kg/m2) and expressed as the mean and SDS. Weight (Wt), height (Ht) SDS and BMI SDS were calculated CDC growth calculator software. All parental height was measured and expressed as mean and standard deviation score. Hormonal data [17-hydroxyprogesterone (17OHP), and testosterone (T)] were recorded. The details of treatment were assessed, including types and average dose of glucocorticoids (cortisone or hydrocortisone). Other relevance investigation radio-imaging (bone age, USG pelvic / testes, CT/ MRI pelvis) and endocrine testing were documented. The time point will be within 4-month interval, whichever closer around the proposed time point if the clinic visit did not actually fall on the proposed visit. Compliance is based on clinical history.

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Pubertal staging was assessed by the method of Marshall and Tanner. Age at puberty was defined at breast Tanner stage 2 in girls and testicular volume >3 ml in boys. Age with pubic hair Tanner stage 2 (age at PH2), age at menarche, and abnormalities in pubertal development such as precocious puberty were assessed. Complications arises during follow up were documented.

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4.4 Definitions

Following definitions applied as below:

1. Salt Wasting (SW)	Genital ambiguity and virilization with salt wasting – hyponatremia (Se Na less than 135 mmol/L, hyperkalemia (Se K > 5mmol/L), inappropriate natriuresis, and low serum and urinary aldosterone with concomitantly high plasma renin (> 47 uU/ml).
2. Simple Virilizing (SV)	They do not able to synthesize cortisol efficiently, but adequate aldosterone secretion remains and thus sodium balance is maintained. Majority presented as genital ambiguity in female; but in male presented late with pseudo-precocious puberty
3. Non-Classical CAH (NC-CAH)	Does not have not have cortisol deficiency, but instead have manifestations of hyperandrogenism hence later presentation in childhood or in early adulthood. Amongst females with NC-CAH will presented with hirsutism and cycle irregularities whereas in male may remain asymptomatic
4. Medical Treatments Minerolocorticoid Glucocorticoids	 Fludrocortisone with dose 100- 200 mcg daily Hydrocortiosone or Cortisone acetate with dose expressed as mg/m2/day
5. Hydrocortisone Dose High Dose	 Hydrocortisone dose ≥ 15mg/m^2/day
Normal Dose	Hydrocortisone dose < 15mg/m^2/day
6. Good Control	The target 17-hydroxyprogesterone range is 12–36 nmol/L when measured in the early morning before medication aiming adequate suppression of 17-OHP (<10nmol/L) or androstenedione concentrations, and that suppression is not achieved by overexposure to cortisol.
7. Final Height (FH)	Height velocity <1cm/year from their previous record or 2 years after completion of puberty (menarche in girls and testicular volume of 15-20 in boys). Patients older than 18 years of age were considered to have reached FH.

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4.5 DATA ANALYSIS

Data was analyzed using Social Package of Statistical Software (SPSS) version 23.

Categorical data will be expressed as frequency with percentages.

Statistical analyses were performed for categorical data using the chi-square test or Fisher exact test. Differences between group of numerical data were with Independent T-test for parametric data between-group comparisons (obesity vs non-obesity with mean GC dose, differences of mean height between cortisone and HCT group).

A P value less than 0.05 was considered statistically significant.

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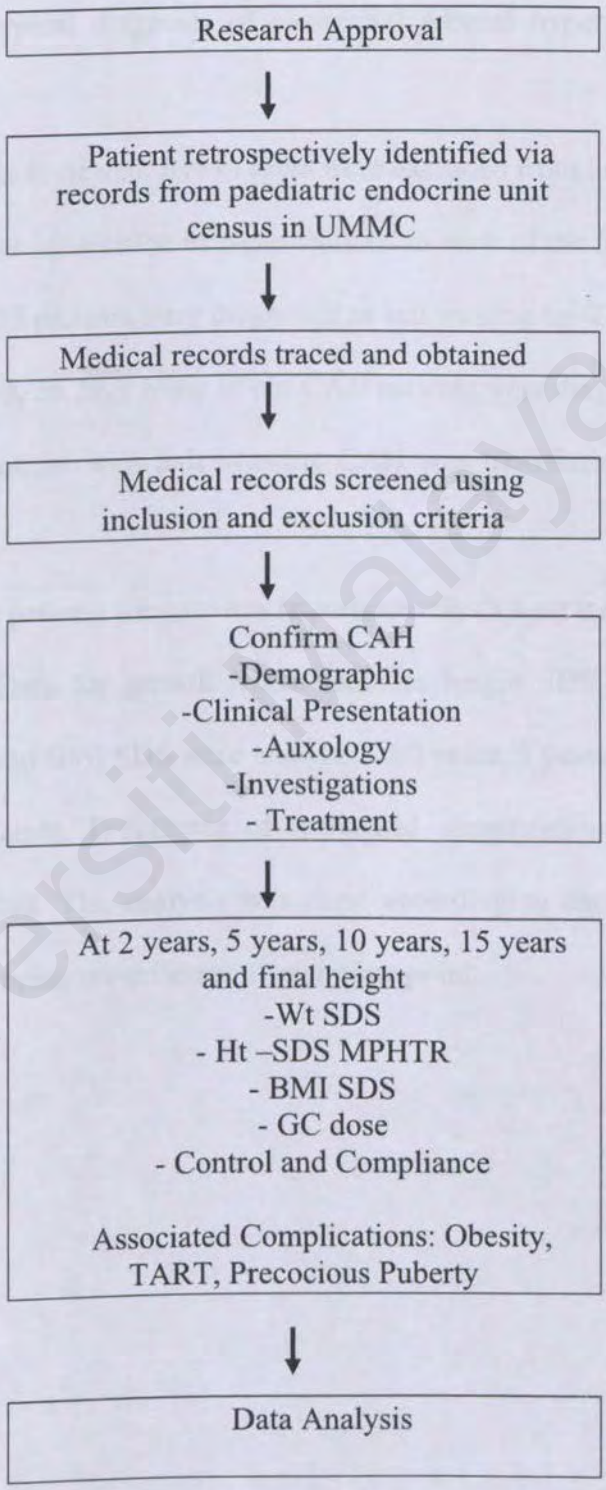
FLOW CHART SHOWING OVERVIEW OF STUDY

Figure 4.1: Flow Chart Overview of study designs



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CHAPTER 5: RESULTS

Based on paediatric endocrine registry in the unit, total of 38 case notes were reviewed fulfilling phenotypical diagnosis of congenital adrenal hyperplasia (CAH) during the study period.

Out of the 38 patients reviewed, five of them were excluded from further analysis of growth outcome and other association in complications in view of the final diagnosis of transient CAH. Total of 33 patients were diagnosed as salt wasting (n=23, 60.5%) and simple virilizing CAH (n=10, 26.3%). None of our CAH patients were diagnosed to have non-classical CAH. One patient with Salt Wasting CAH was transferred to different center.

The remaining of 32 patients were review retrospectively data on their growth and associated complications. Data for growth which includes height SDS, mid-parental target height SDS, weight and BMI SDS were analyzed at 2 years, 5 years, 10 years, 15 years and at their final height. Prevalence of associated complications and related association were documented. The analysis was done according to data availability; therefore, the number of samples are different at each time point.

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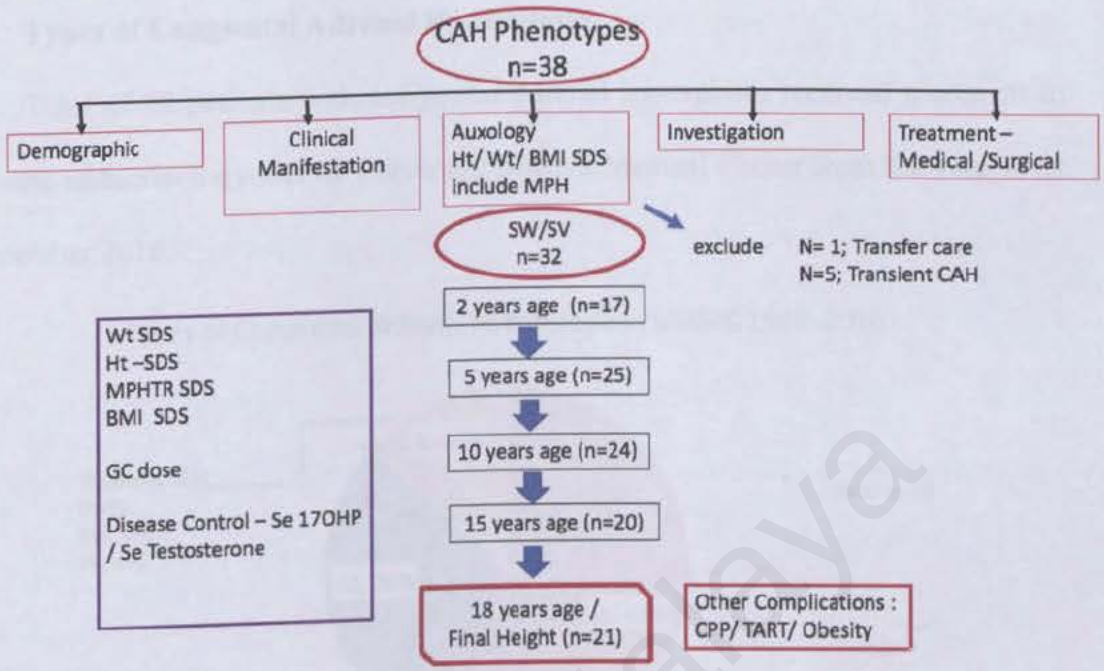
Figure 5.1: FLOW CHART OUTCOME STUDY



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5.1: PREVALENCE OF CONGENITAL ADRENAL HYPERPLASIA in UMMC

5.1.1 Types of Congenital Adrenal Hyperplasia

Total of 38 patients with congenital adrenal hyperplasia received treatment in paediatric endocrinology unit of University Malaya Medical Center from the year 1982 to December 2016.

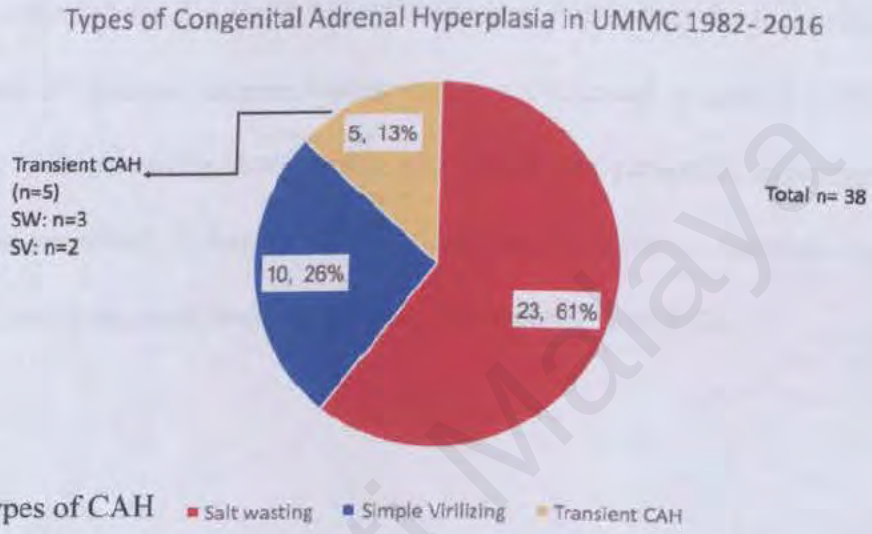

Fig 5.2: Types of CAH

All of them were classified as Classical CAH and none of these patients were thought to be non-classical CAH. Amongst classical CAH, 68.7% of the patients were initially classified to salt wasting (n= 26) and another 31.6% was simple virilizing (n=12). However, 5 of the patients (n=3 from salt wasting and n=2 from salt simple virilizing group) were excluded because of the possibility of 'transient CAH'. They seem to show persistently low serum 17-OHP and testosteronee levels despite on low dose of mineralocorticoid and glucocorticoids. Synacthen test was subjected to these group of patient for confirmation. All of them (n=5) showed a completely normal 17OHP and cortisol levels following the stimulation test.

Therefore; the prevalence of types of CAH seen in UMMC are 60.5% (n= 23) in salt wasting group, 26.3% (n= 10) in simple virilizing and 13.2 % (n=5) are labelled transient CAH. See Fig 5.2.

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5.1.2 Prevalence of CAH by enzyme diagnosis

Due to minimal funds availability, most children with CAH seen in UMMC did not have genetic testing done. Diagnosis was made mostly from clinical presentation and hormonal investigation. Majority of them n= 35 (92 %) were suspected to have 21-hydroxylase deficiency. Two siblings (5.3%) presented with salt wasting and ambiguous genitalia (undervirilized male) and had low serum 17-OHP and serum testosterone. They were suspected to have 3-β Hydroxylase deficiency. Fortunately for these two, we were able to send for genetic enzyme testing and was confirmed to have 3-β Hydroxylase deficiency. One patient presented with virilization and persistent hypertension. This patient was suspected to have 11-β Hydroxylase Deficiency. However, no genetic enzymatic testing was sent due to financial restrictions (Figure 5.3).

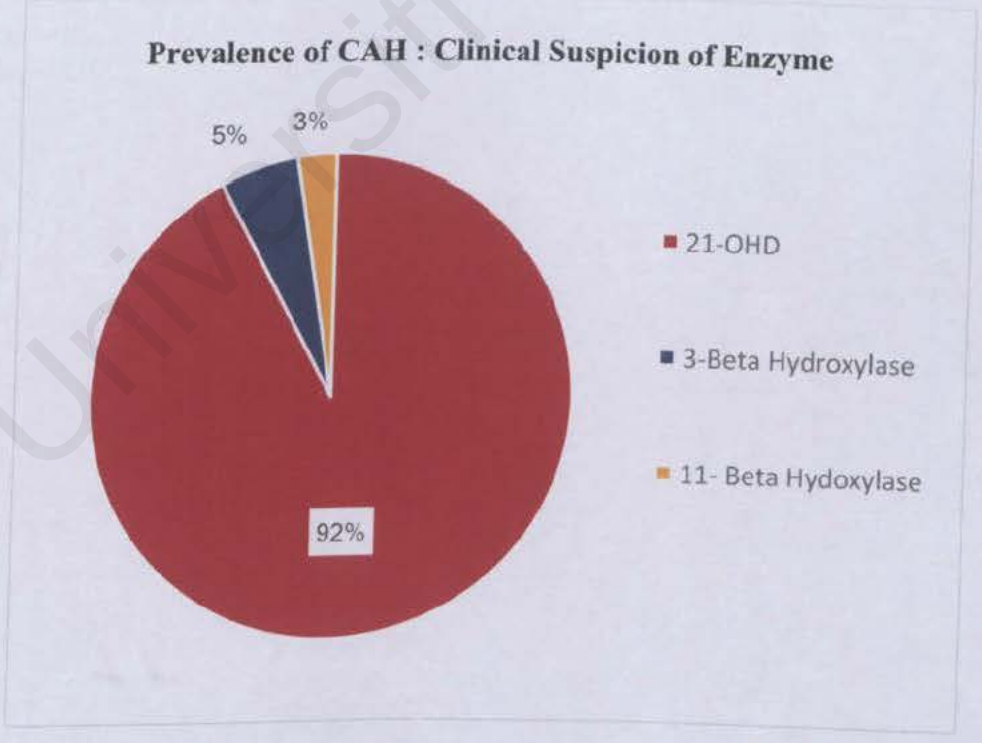

Figure 5.3: Prevalence of CAH by enzymes deficiency

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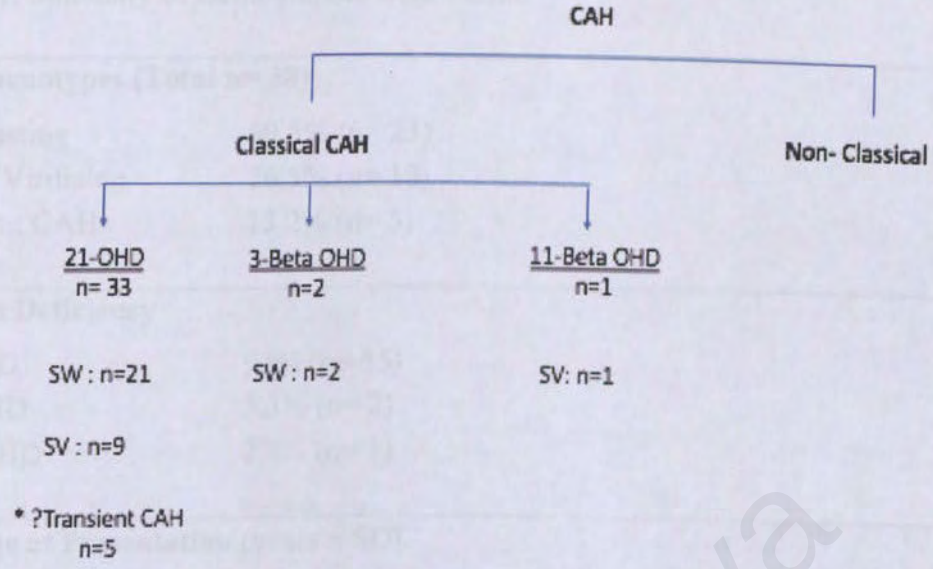

Figure 5.4: Summary of CAH types by enzyme diagnosis

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Table 5.1: Summary of Demographic Distribution

CAH Phenotypes (Total n= 38)		
Salt Wasting	60.5% (n= 23)	
Simple Virilizing	26.3% (n= 10)	
Transient CAH	13.2% (n= 5)	
Enzymes Deficiency		
21-OHD	92% (n= 35)	
3-β OHD	5.3% (n= 2)	
11-β OHD	2.7% (n= 1)	
Mean Age at Presentation (years ± SD)		
Salt Wasting	Male: 0.08 ± 0.07 (n=13)	Female: 0.06 ± 0.04 (n= 13)
Simple Virilizing	Male: 4.3 ± 3 (n= 2)	Female: 1.8 ± 1.7 (n= 10)
Gender Distribution		
Salt Wasting	Male: n=12	Female: n= 11
Simple Virilizing	Male: n= 2	Female: n= 8
Transient CAH	Male: n= 1	Female: n= 4
Ethnicity		
Malay	39.5% (n= 15)	
Chinese	39.5% (n= 15)	
Indian	18.4% (n= 7)	
Others	2.6% (n= 1)	

Total = n

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5.2 DEMOGRAPHIC DISTRIBUTION AT PRESENTATION

5.2.1 Age at Presentation

A total of 38 patients with congenital adrenal hyperplasia under follow up with paediatric endocrinology unit of University Malaya Medical Center were reviewed. Mean age of presentation was 0.76 ± 1.5 years ranging from birth to 6.54 years old. *See Table 5.2.*

Table 5.2: Summary of mean age at presentation

	CAH Diagnosis	
	Salt Wasting (n)	Simple Virilizing (n)
Male	0.08 ± 0.07 (n=13)	4.3 ± 3 (n=2)
Female	0.06 ± 0.04 (n=13)	1.8 ±1.7 (n=10)

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Majority 60.5% were female (n=23) and 39.5% were male (n=15). 78.9% of them presented within the first 6 months of life (female; n=17 and male; n=13). Two of them presented later at 6.5 years old and 4.1 years old (Figure 5.5).

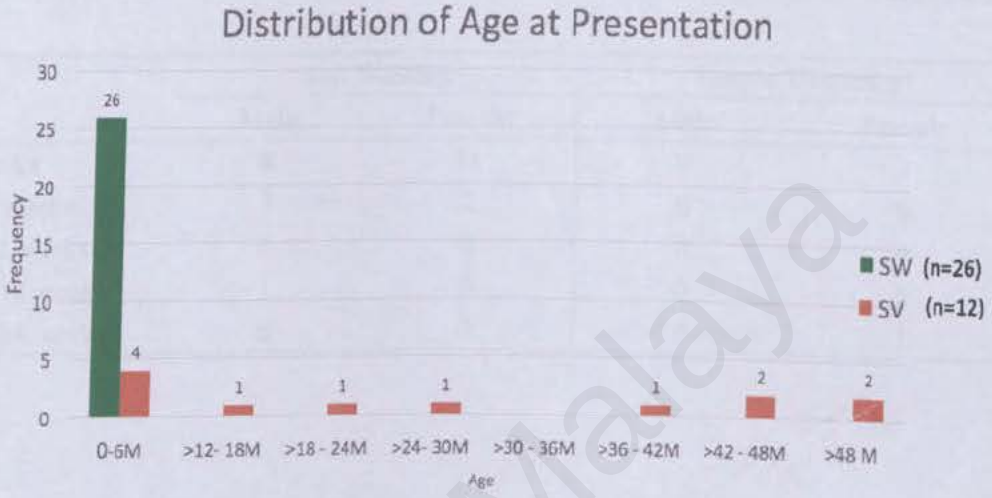

Figure 5.5: Distribution of age at presentation among CAH phenotypes

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All children with salt wasting CAH presented before 6 months old (less than 24 weeks old). All female with salt wasting CAH were diagnosed within 6 weeks of life as compared to male children who were diagnosed later at 12- 18 weeks old. See Table 5.3.

Table 5.3: Distribution of CAH diagnosis with age at presentation (less than 24 Weeks old)

	Salt Wasting		Simple Virilizing	
	Male	Female	Male	Female
0- 3weeks	**8**	**11**	0	3
> 3 - 6 weeks	3	2	0	0
> 6 - 12 weeks	1	0	0	0
> 12 – 18 weeks	1	0	0	0
> 18 – 24 weeks	0	0	0	1

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5.2.2 CAH by Gender Distribution

Female children comprise majority 60.5% (n=23) of total CAH patient compared to male (n=15, 39.5%). Among the female children, 47.8% were diagnosed as salt wasting (n=11), 34.8% with simple virilizing (n=8) and 17.4% most probably had transient CAH (n=4). See Figure 5.6.

Among the males; 12 from 15 of them were diagnosed with salt wasting (80%) compares to 13.3% who had simple virilizing (n=2) and 6.7% had transient CAH (n=1). Figure 5.7.

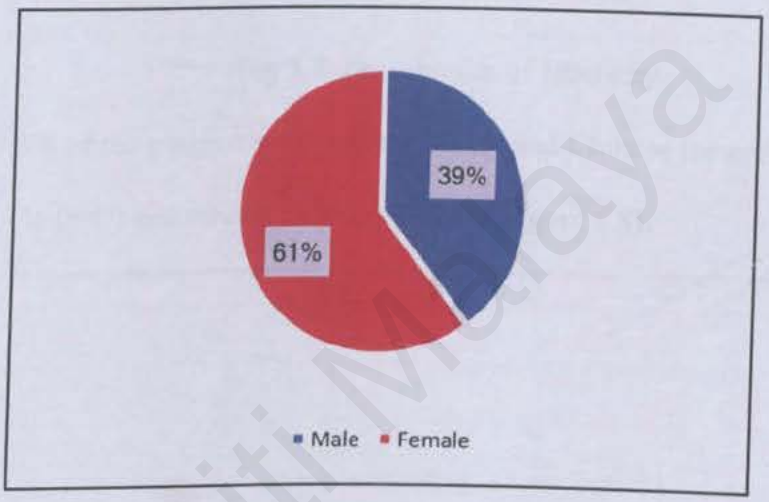

Figure 5.6: Total CAH by gender

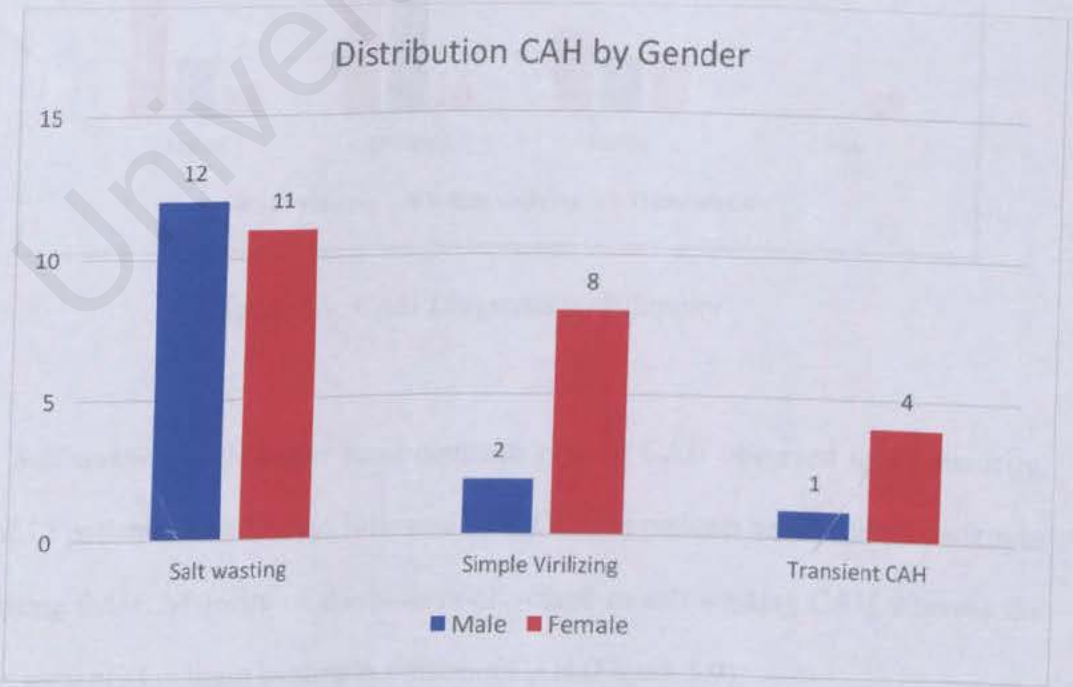

Figure 5.7: Types of CAH by gender

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5.2.3 *Ethnicity*

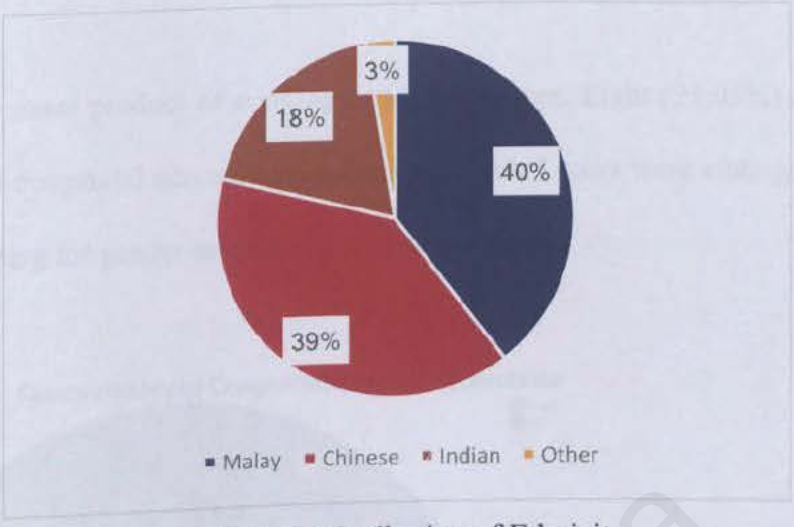

Fig 5.8: Distribution of Ethnicity

Majority 39.5% of the patients were among Malay and Chinese for each (n=15), Indian race was 18.4% (n=7) and other's race was only 1 (Figure 5.8).

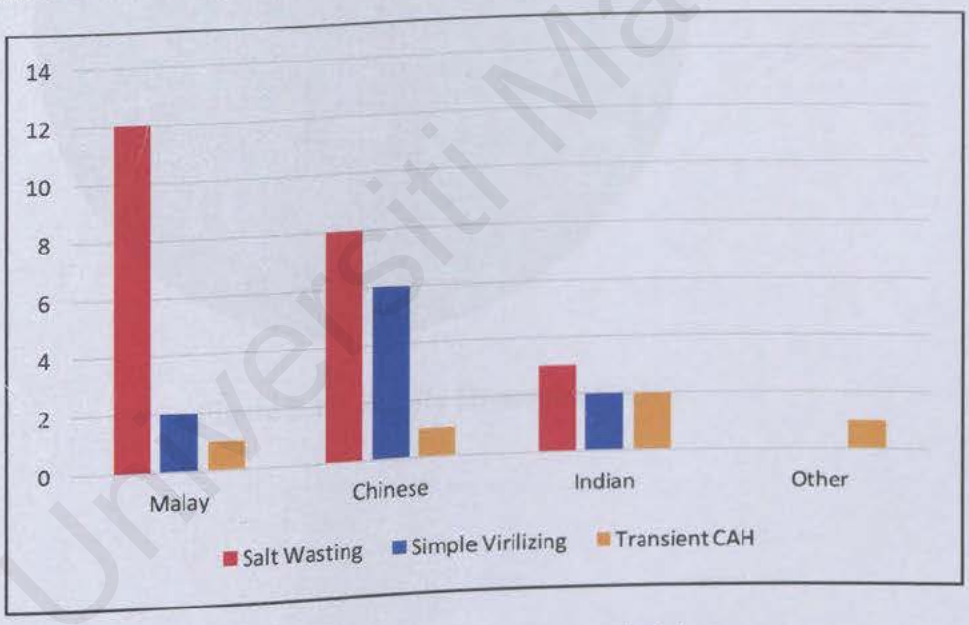

Figure 5.9: CAH Diagnosis by Ethnicity

Salt wasting CAH is the most common type of CAH observed in all ethnicity. Total of 12 patients were Malay, followed by 8 Chinese patients and 1 Indian patient in salt wasting CAH. Majority of the Malays presented as salt wasting CAH whereas the Chinese were predominant in simple virilizing CAH (Figure 5.9).

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5.2.4 *Family History*

There were 3 cases product of consanguineous marriage. Eight (21.05%) cases had family history of congenital adrenal hyperplasia in which 3 pairs were siblings. All patients had karyotyping for gender assessment (Figure 5.10).

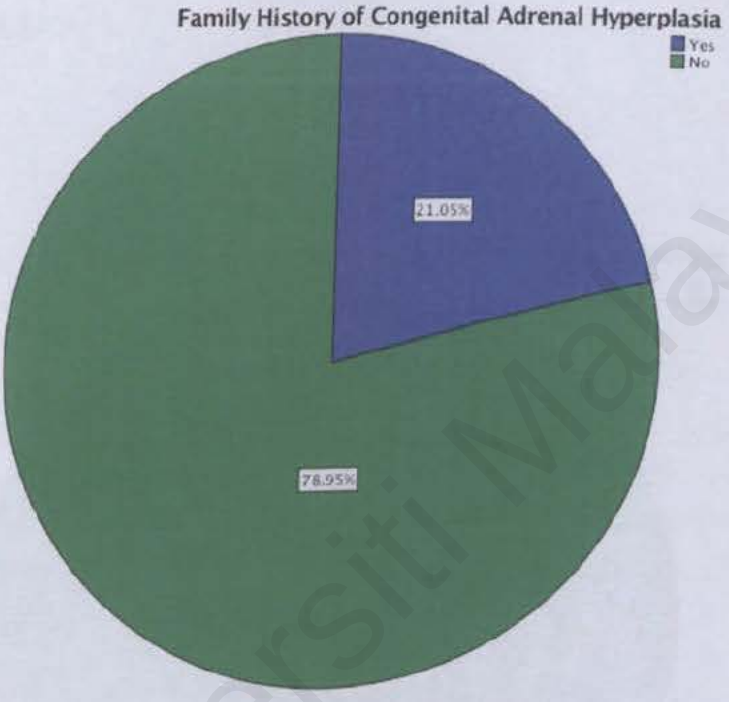

Figure 5.10: Family History of CAH

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5.2.5 Current Follow Up Status

Currently total of 21 patients (55.3%) are still under our paediatric endocrinology outpatient follow up. The remaining 17 patients were either transferred to adult care (n=13, 76.4%), transferred to another hospital (n=2, 11.8%), 1 of them defaulted and 1 has been discharged- 5.8%. No mortality was reported among our cohort of patients (Figure 5.11).

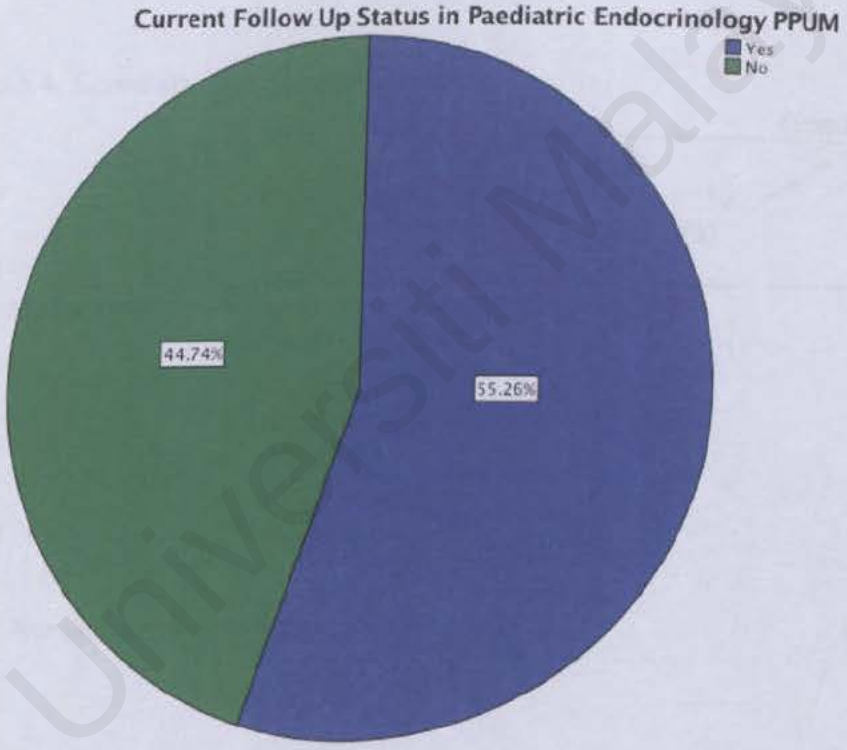

Figure 5.11: Current Follow Up Status in UMMC

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5.3 At Presentation

5.3.1 Clinical Presentation

31.6% of the patient presented as salt losing crisis (n=12). Male children predominantly presented this way (n=10, 26.3%). There were also mixed of clinical presentation being as salt losing and virilization (n=9, M=1;2.6%, F=8;21.1%) or with salt losing and genitalia ambiguity (n=2; female (5.3%). Eight patients presented after age of 1 year old (n=8) had virilization at diagnosis. Summary of clinical manifestation at diagnosis in relation to age of onset and gender are as below (Table 5.4):

Table 5.4: Summary of Clinical Presentation

		Gender	
	Clinical Presentation	Male n=15 (39.5%)	Female n=23 (60.5%)
Onset			
Before age 1 year	**SW only**	**10**	**2**
	SW + Virilization	1	**8**
	SW + Ambiguous	0	2
	Virilization	2	2
	Ambiguous	0	2
	Hyperpigmentation	0	1
After >1 year	Virilization	2	6

SW- Salt Wasting, M= Male, F= Female

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5.3.2 Biochemical Parameters at Presentation

At presentation, majority of our patient had raised Se 17- hydroxyprogesterone level of more than 60.6 nmol/L with median 201.95 nmol/L (n=22, IQR 578) and Se testosterone 7.9 nmol/L with IQR 24.38 (n=22). 60% developed hyponatremia with median of serum sodium of 126.5 mmol/L (n=18, IQR18) and hyperkalemia among 24 (82.4%) of them with median potassium at presentation was 6.1mmol/L (IQR 1.7). Table 5.12 and 5.13.

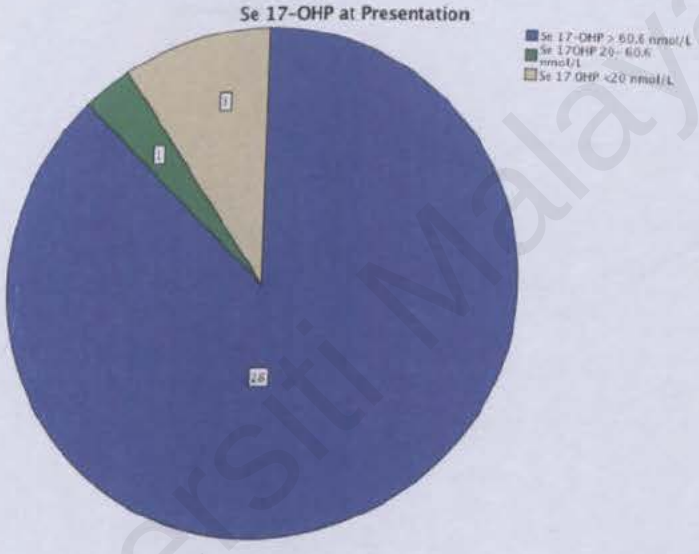

Fig 5.12: Serum 17-OHP at presentation

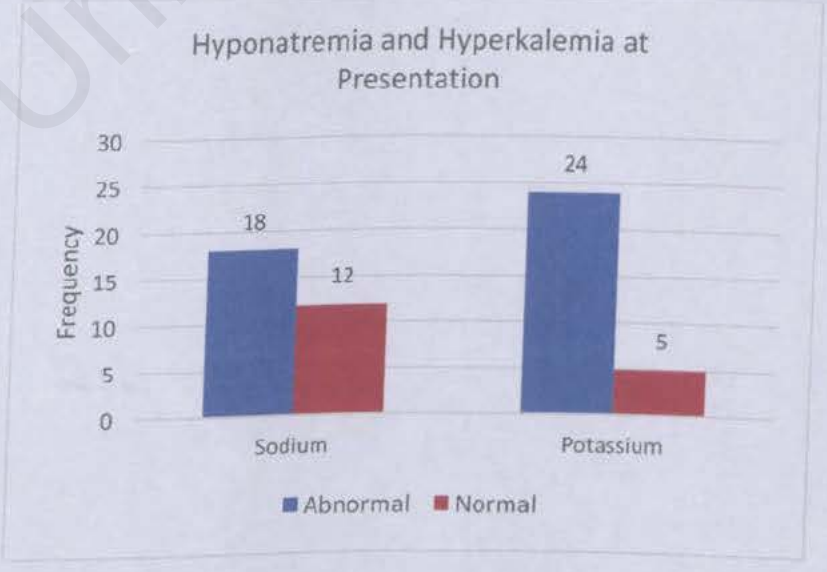

Fig 5.13: Electrolytes abnormality at presentation

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5.3.3 Treatment at Diagnosis

Cortisone acetate was started in 10 of our patient (26.3%) at diagnosis before year 1996 prior to the availability of hydrocortisone tablets in Malaysia. Median dose given was 30 mg/m2/day; IQR 46.25. All of those started with cortisone were subsequently changed to hydrocortisone tablets once it made available in Malaysia. The rest of the patients (n=28) were started with hydrocortisone. Mean dose of hydrocortisone at initiation was at 15.3 ± 3.4 mg/m2/day; Fludrocortisone supplement was prescribed for 19 of the patients with median dose of 100 mcg/day (IQR 50).

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5.3.4 Surgical intervention

Total of 19 from 38 patients (50%) had undergone genitalia corrective surgery with mean age of surgery was at 2.7 ± 2.3 years. Types of corrective surgery done includes Clitoroplasty (n=13), Feminizing Genitoplasty (n=3) and Orchidopexy followed by hypospadias surgery (n=2). *Figure 5.14*

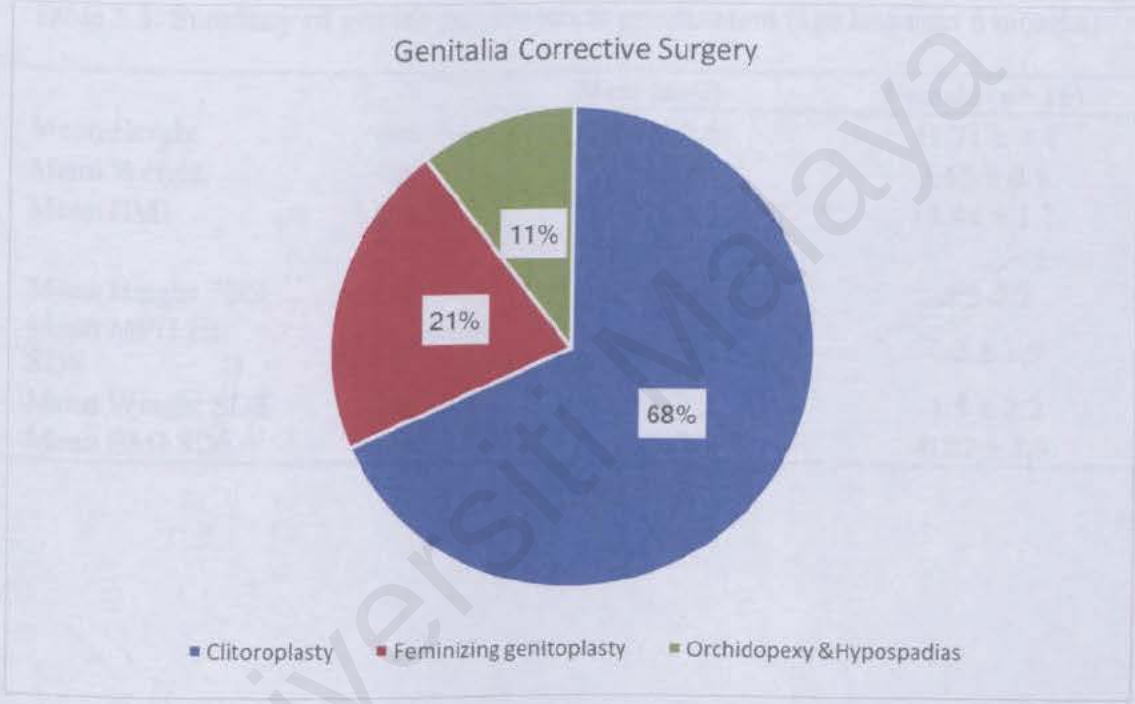

Figure 5.14: Genitalia corrective surgery

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5.4 GROWTH OUTCOME OF CHILDREN DIAGNOSED WITH CAH

5.4.1 Growth of Children at Presentation

Total of 38 patients were reviewed for growth at their presentation. We have found that the weight and BMI SDS was markedly lower in boys most probably that due to salt wasting crisis that majority of this group had at presentation. Summary of growth were as Table 5.5.

Table 5.5: Summary of growth parameters at presentation (age less than 6 months)

		Male (n=9)	Female (n= 16)
Mean Height	cm	59.52 ± 7.6	51.71 ± 4.4
Mean Weight	kg	5.0 ± 2.6	3.65 ± 0.9
Mean BMI	kg/m^2	13.37 ± 4.7	13.44 ± 1.7
Mean Height SDS	cm	-0.1 ± 1.9	-1 ± 2.2
Mean MPH Ht SDS	cm	0.49 ± 1.8	-0.2 ± 1.9
Mean Weight SDS	kg	-1.66 ± 2.3	-1.5 ± 2.2
Mean BMI SDS	kg/m^2	-2.51 ± 3.4	-0.87 ± 1.5

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5.4.2 Growth of Children at age 2 years old

A total of 17 patients had growth parameters available for analysis at 2 years age. Eight from 17 children were male and nine were female. Amongst these 17 children, six of them received cortisone acetate (n= 4; male and n= 2; female) and another eleven children received hydrocortisone therapy (n= 4; male and n=7; female). *Table 5.6.*

Table 5.6: Summary of growth parameters at age 2 years old

		Male (n=8)	Female (n=9)
Mean Height	cm	84.16 ± 6.5	82.75 ± 2.8
Mean Weight	kg	11.21 ± 1.9	10.71 ± 1.0
Mean BMI	kg/m^2	15.72 ± 1.2	15.64 ± 1.4
Mean Height SDS	cm	-0.55 ± 1.7	-0.73 ± 0.8
Mean MPH Ht SDS	cm	-0.06 ± 1.5	0.60 ± 0.7
Mean Weight SDS	kg	-0.61 ± 1.8	-1.31 ± 1.0
Mean BMI SDS	kg/m^2	-0.71 ± 1.3	-0.88 ± 1.1

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For the male children (n=8), their mean height was 84.16 ±6.5 cm compared to female at 82.75 ±2.8 cm (n=9). Their mean height SDS was at -0.55 ±1.7 cm for male and -0.73 ± 0.8 cm for female which was within normal compares to standard population and mid parental height SDS was at -0.06 ±1.5 cm and -0.60 ± 0.7 cm for each male and female. *Figure 5.15 and 5.16*

Figure 5.15: Mean Height SDS at 2 years

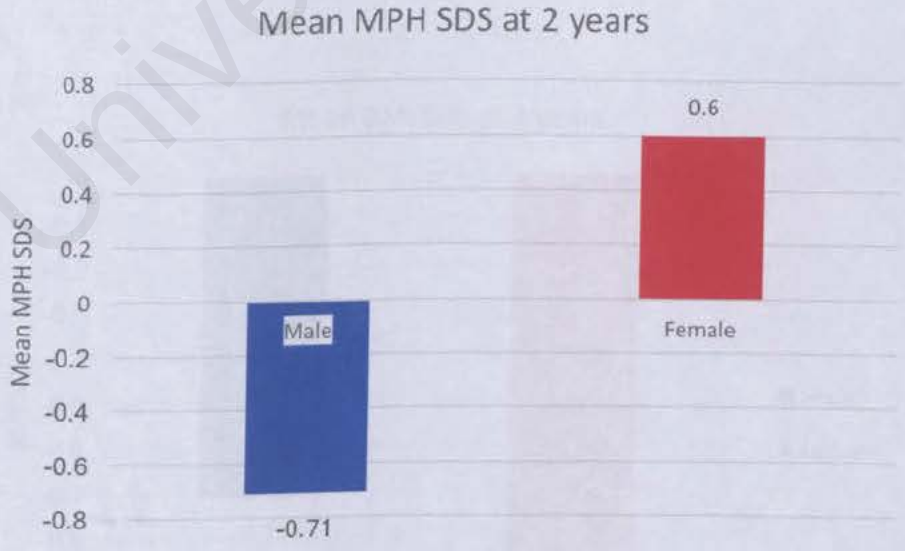

Figure 5.16: Mean MPH SDS at 2 years

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In regards of weight, the male weights were 11.21 ±1.9 kg with weight SDS of -0.61 ±1.8 compared to female 10.71 ± 1.0kg (Figure 5.17). The mean BMI for both gender was within normal BMI SDS with BMI SDS for male was -0.71 ±1.3 and -0.88 ± 1.1 among female (Figure 5.18).

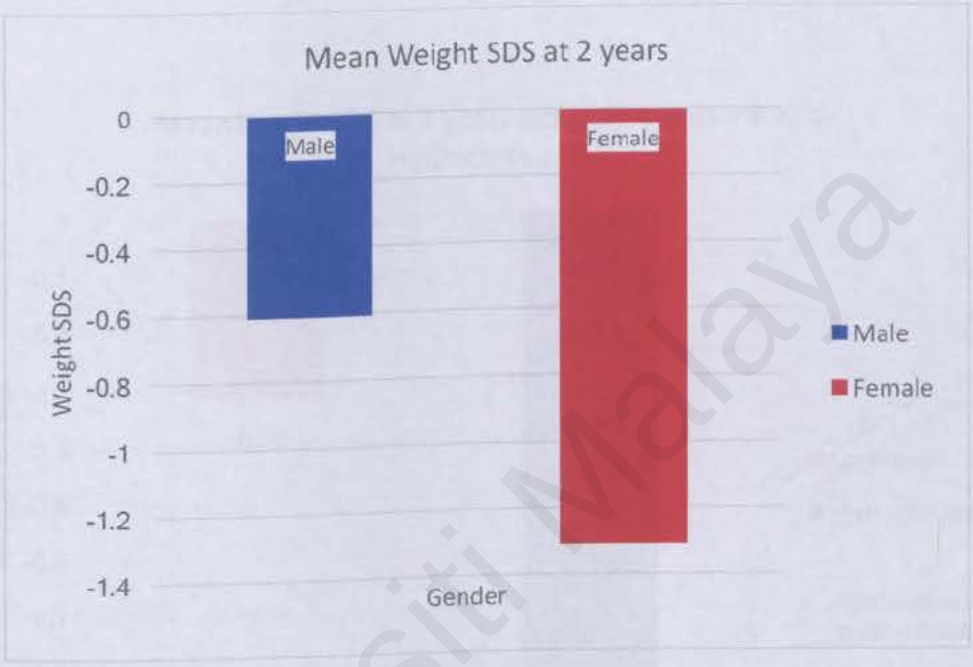

Figure 5.17: Mean Weight SDS at 2 years

Figure 5.18: Mean BMI SDS at 2 years

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Comparing between those who were treated with cortisone and hydrocortisone, the mean height SDS was -0.32 cm ± 1.5 and -0.83 cm ± 1.3 for each group. Total of six patients received cortisone acetate and another 11 patients were on hydrocortisone. No significant differences between mean height SDS among those with cortisone and hydrocortisone with p-value of 0.466. *Figure 5.19*

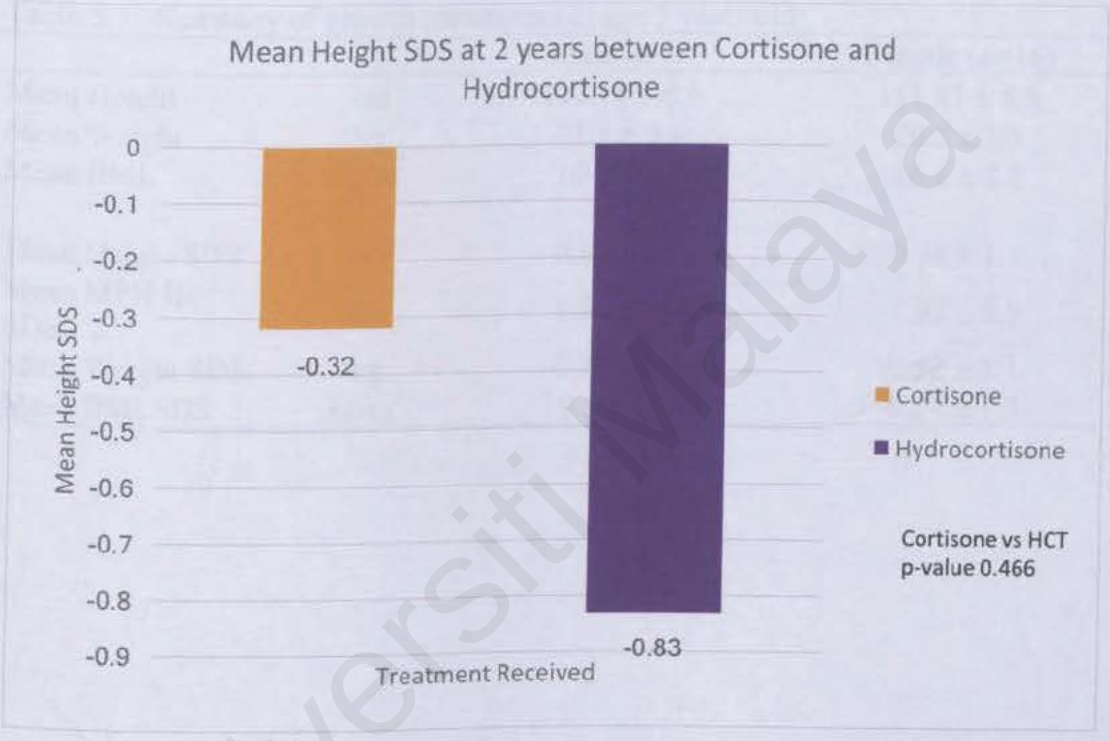

Figure 5.19: Mean Height SDS at 2 years between cortisone and HCT

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5.4.3 Growth of Children at 5 years old

At 5 years old time point review, a total of 25 patients were reviewed for growth analysis. Nine of them were male and another 16 patients were female. Majority of them were on hydrocortisone (n=19) and the remaining six was on cortisone acetate. *Table 5.7*

Table 5.7: Summary of growth parameters at age 5 years old

		Male (n=9)	Female (n=16)
Mean Height	cm	112.11 ± 6.6	111.83 ± 5.8
Mean Weight	kg	21.1 ± 5.1	20.2 ± 3.3
Mean BMI	kg/m^2	16.6 ± 2.8	16.1 ± 2.2
Mean Height SDS	cm	0.87 ± 1.1	0.83 ± 1.1
Mean MPH Ht SDS	cm	1.64 ± 1.4	1.93 ± 0.9
Mean Weight SDS	kg	0.77 ± 1.8	0.52 ± 1.1
Mean BMI SDS	kg/m^2	0.5 ± 1.8	0.24 ± 1.3

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There is an increment of mean height observed from 2 years to 5 years old. At 5, the males were 112.11 ± 6.6 cm and the females were 111.83 ± 5.8 cm. The mean height SDS has improved at this point, with mean height SDS of 0.87 ± 1.1 in males and 0.83 ± 1.1 in females (Figure 5.20). The mean mid-parental height SDS was 1.64 ±1.4 cm in males and 1.93 ± 0.9 cm in females (Figure 5.21).

Figure 5.20: Mean Height SDS at 2 and 5 years

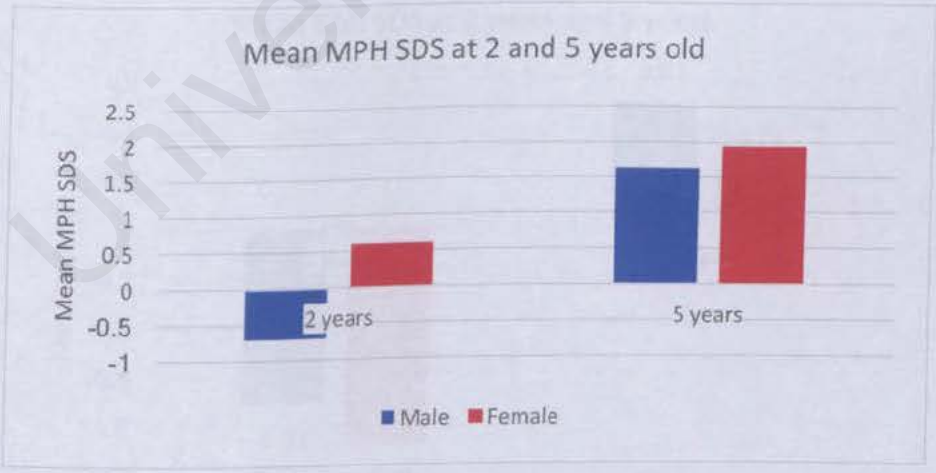

Figure 5.21: Mean MPH SDS at 2 and 5 years

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No difference observed in regards of mean weight among males and females with 21.1± 5.1kg and 20.2 ± 3.3 kg for each group. The mean weight SDS was 0.77 ± 1.8 in males and 0.52 ± in females (Figure 5.22). The BMI was within normal with mean BMI of 16.6 ± 2.8 kg/m^2 in males and 16.1 ± 2.2 kg/m^2 in females. The mean BMI SDS for males and females were 0.5 ±1.8 and 0.24 ± 1.3 respectively (Figure 5.23).

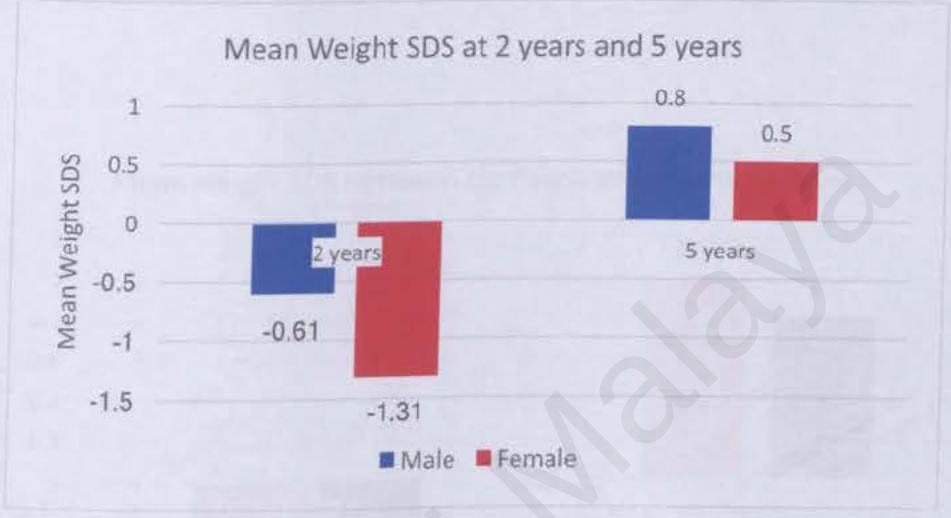

Figure 5.22: Mean Weight SDS at 2 years and 5 years

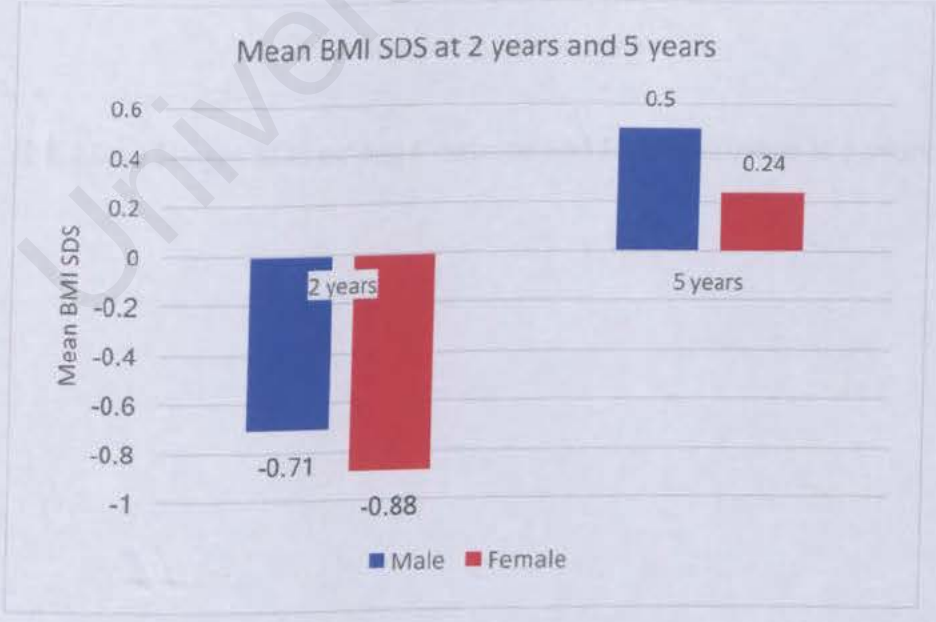

Figure 5.23: Mean BMI SDS at 2 years and 5 years

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Between the group of children that was treated with cortisone (n=6) and hydrocortisone (n=19), there were no significant association seen [p-value of 0.757]. The mean height SDS was 0.98 ± 1.2 cm in those with cortisone and 0.81 ± 1.1 cm in hydrocortisone (Figure 5.24).

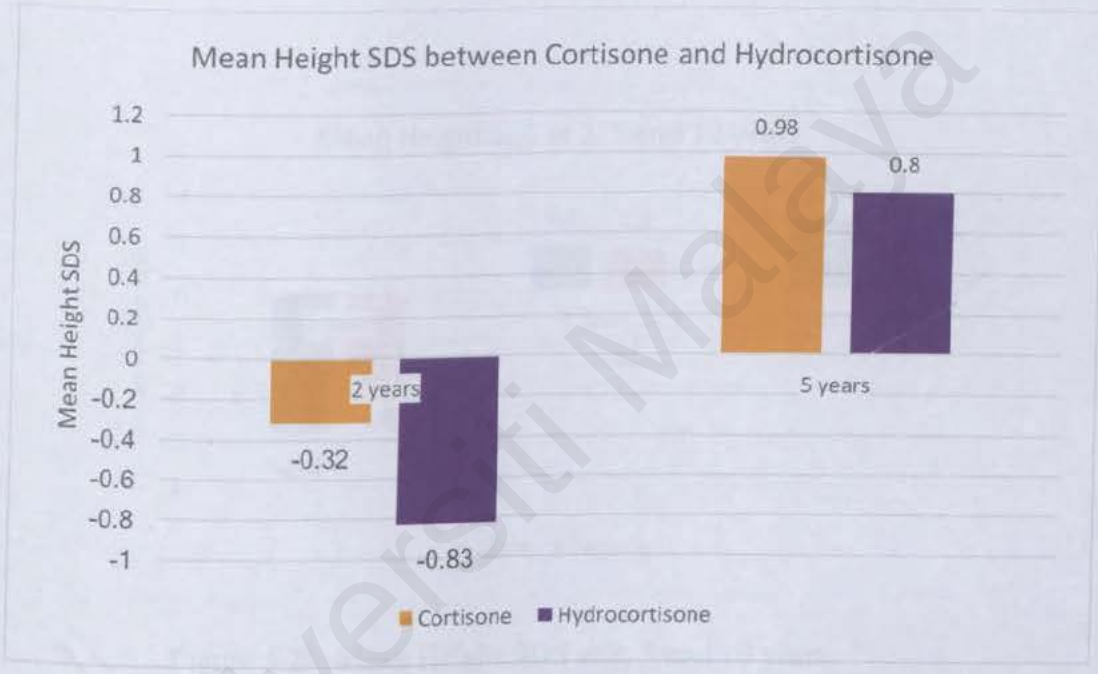

Figure 5.24: Mean Height SDS among Cortisone and Hydrocortisone at 5 years old

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5.4.4 Growth of Children at 10 years old

A total of 24 patients were reviewed for growth analysis at 10 years old time-point. There were 10 males and 14 female patients. Mean height for each gender was 146 ± 6.4 cm for males and 141.9 ± 6.1 cm for females. Height SDS showed further increment at this age with height SDS in male was 1.41 ± 0.9 cm and 0.96 ± 1.0 cm in female (Figure 5.25 and 5.26).

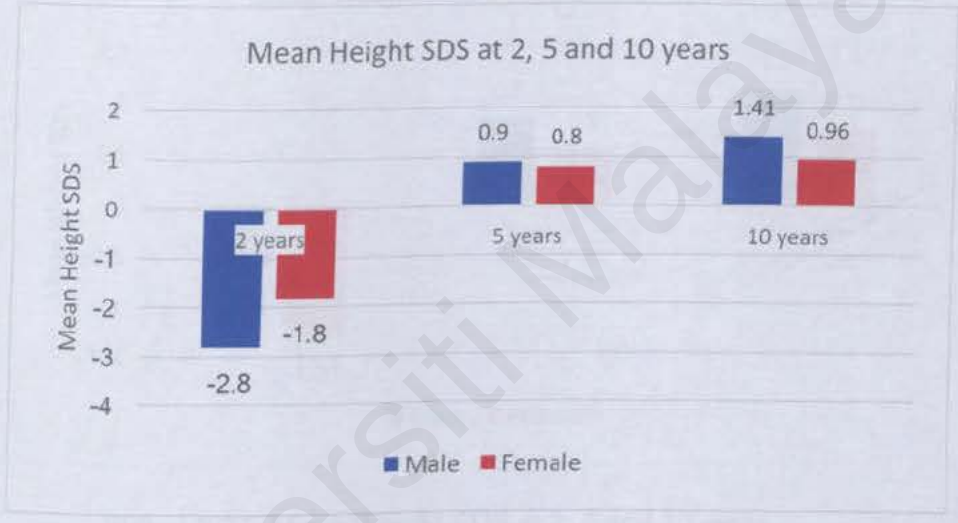

Figure 5.25: Mean Height SDS at 2, 5 and 10 years.

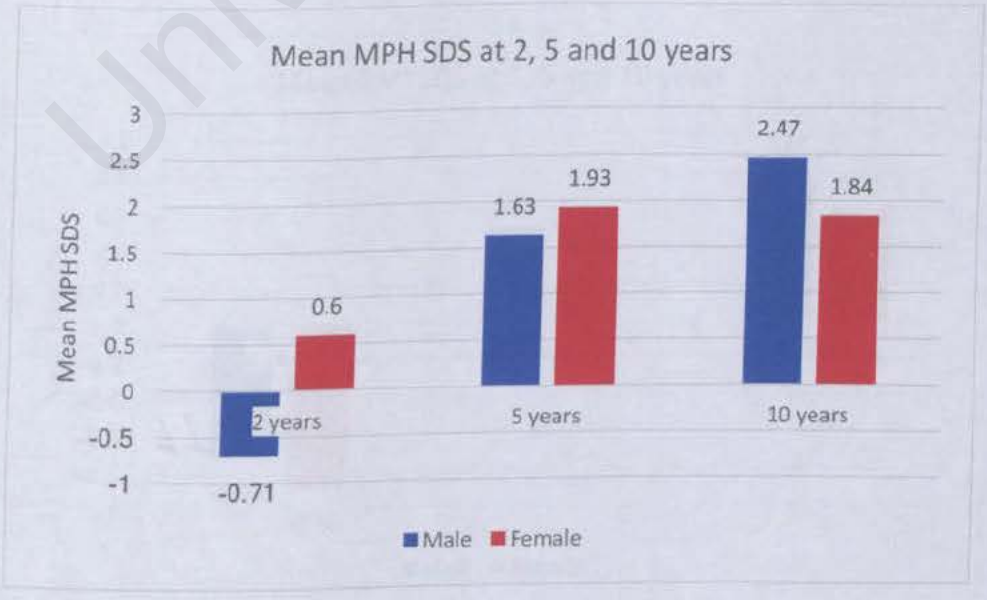

Figure 5.26: Mean MPH SDS at 2, 5 and 10 years

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Mean weight was 39.2 ± 5.9 kg among males and 37.5 ± 4.9 kg in females. The mean weight SDS was 1.10 ±0.7 in males and 0.71 ± 0.6 kg in females (Figure 5.27). The mean BMI was still within the normal range; 18.3 ± 2.1 kg/m^2 in males and 18.5 ± 1.9 kg/m^2 in females. The mean BMI SDS for males and females was 0.79 ± 0.9 kg/m^2 and 0.59 ± 0.7 kg/m^2 (Figure 5.28).

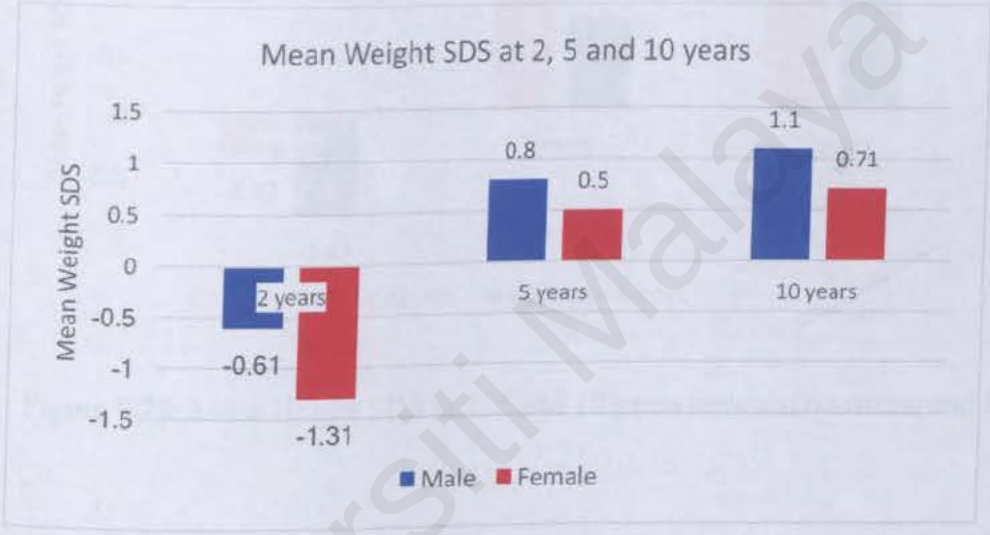

Figure 5.27: Mean Weight SDS at 2, 5 and 10 years

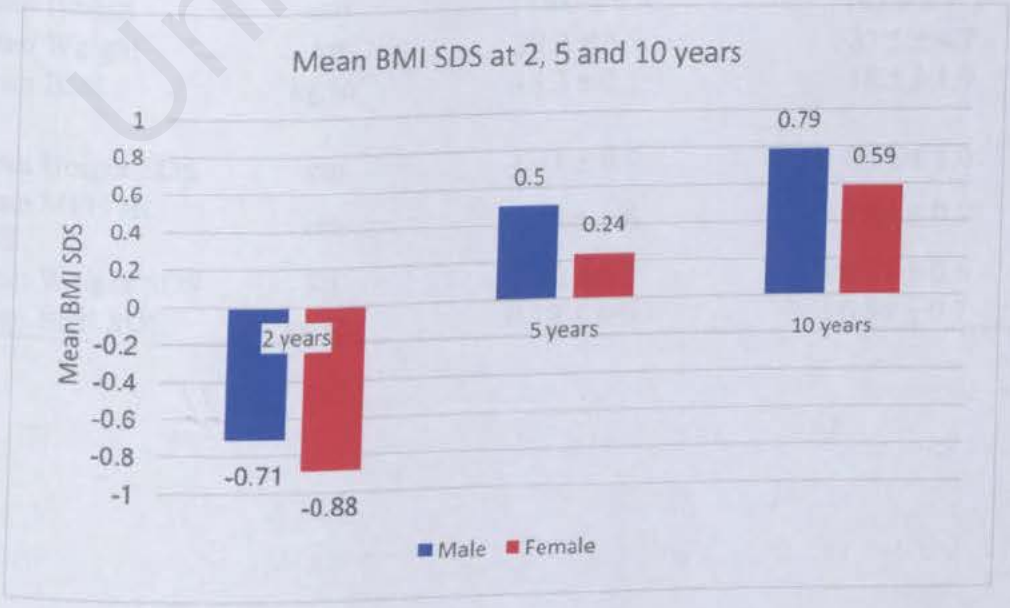

Figure 5.28: Mean BMI SDS at 2, 5 and 10 years

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Nine out of 24 patients were initially treated with cortisone acetate and the remaining 15 patients were treated with hydrocortisone only. The mean height SDS in cortisone acetate was 1.3 ± 0.9 cm and 1.1 ± 1.1 cm among hydrocortisone group. There was no significant different statistically with p- value of 0.569 (Figure 5.29).

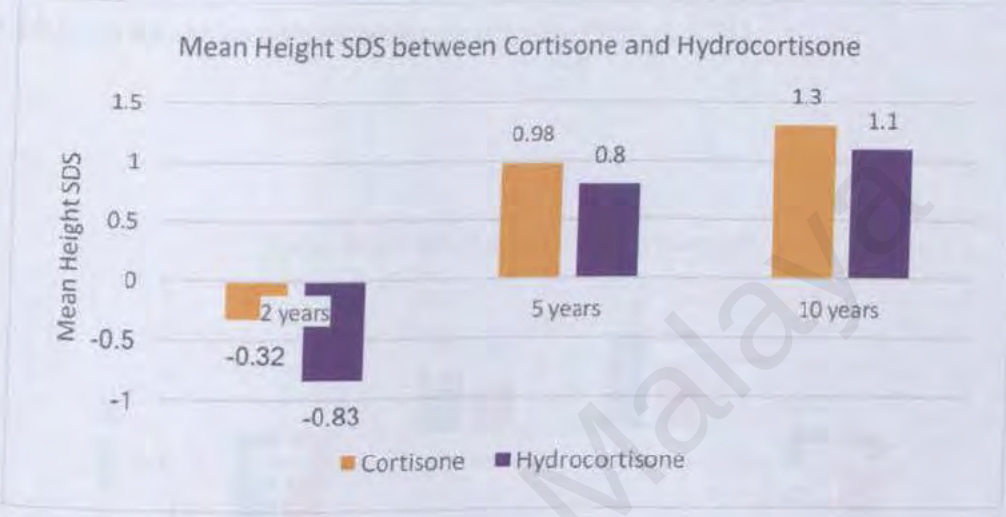

Figure 5.29: Mean Height SDS at 2, 5 and 10 years between cortisone and HCT

Table 5.8: Summary of growth parameters at age 10 years old (Total n= 24)

		Male (n=10)	Female (n=14)
Mean Height	cm	146.0 ± 6.4	141.9 ± 6.1
Mean Weight	kg	39.2 ± 5.9	37.5 ± 4.9
Mean BMI	kg/m^2	18.3 ± 2.1	18.5 ± 1.9
Mean Height SDS	cm	1.41 ± 0.9	0.96 ± 1.0
Mean MPH Ht SDS	cm	2.48 ± 1.6	1.84 ± 0.9
Mean Weight SDS	kg	1.10 ±0.7	0.71 ± 0.6
Mean BMI SDS	kg/m^2	0.79 ± 0.9	0.59 ± 0.7

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5.4.5 Growth of Children at 15 years old

Total of 20 patients were reviewed for the time point at 15 years age. Eight from 20 patients were males and 12 were females. Mean height was 159.9 ± 7.3 cm for males and 152.3 ± 8.9 cm for females. Height SDS for males were -0.55 ± 7.3 cm and females were -1.37 ± 1.5 cm (Figure 5.30). Mid-parental height SDS was -0.02 ± 0.6 cm and -0.75 ±1.6 cm for males and females respectively (Figure 5.31).

Figure 5.30: Mean Height SDS at 2, 5 ,10 and 15 years

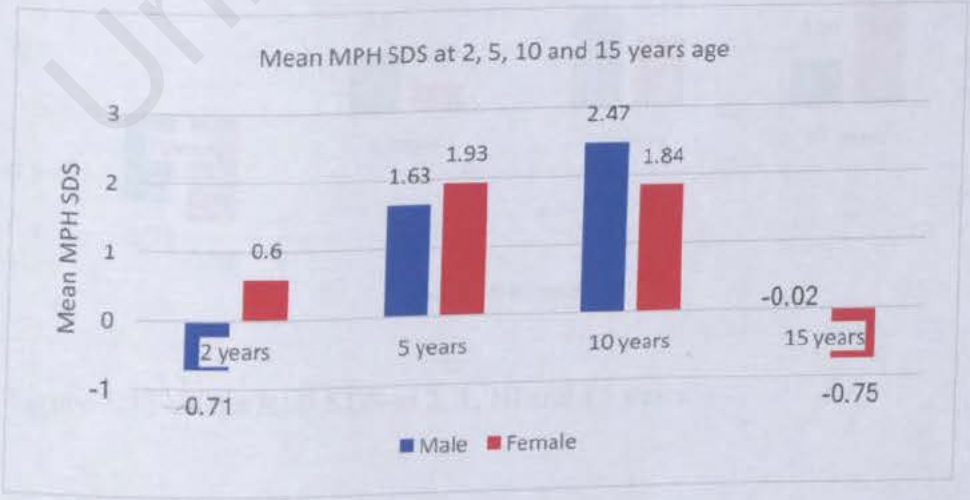

Figure 5.31: Mean MPH SDS at 2, 5, 10 and 15 years

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The mean weight was 53.2 ± 10 kg in males and 53.9 ± 8.5 kg among females with mean weight SDS -0.22 ± 1.1 kg in males and 0 ± 0.9 in females (Figure 5.32). BMI SDS was within the normal range with BMI SDS in males were 0.39 ± 1.3 kg/m^2 and 0.97 ± 0.9 kg/m^2 in females (Figure 5.33).

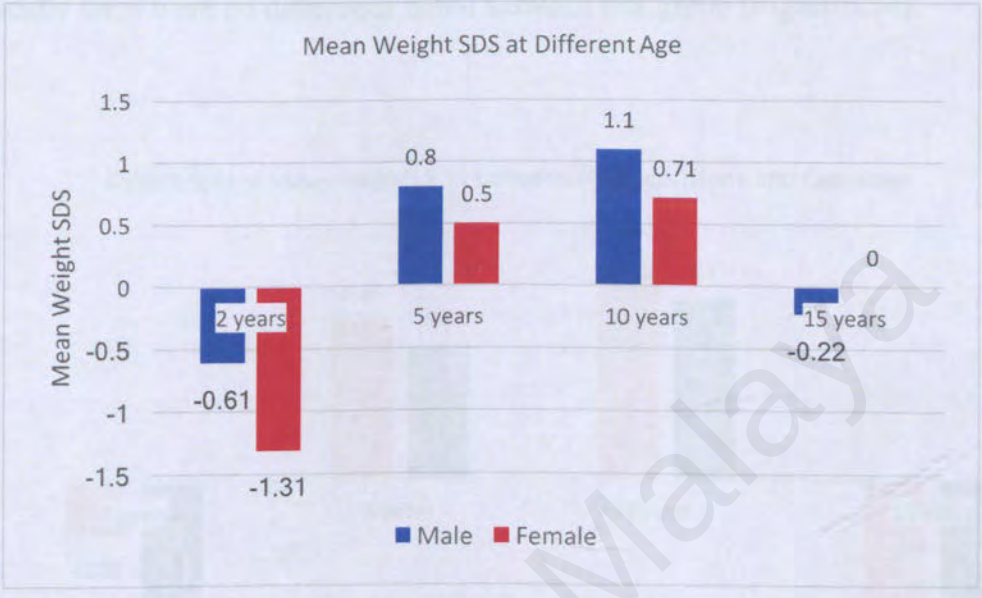

Figure 5.32: Mean Weight SDS at 2, 5, 10 and 15 years

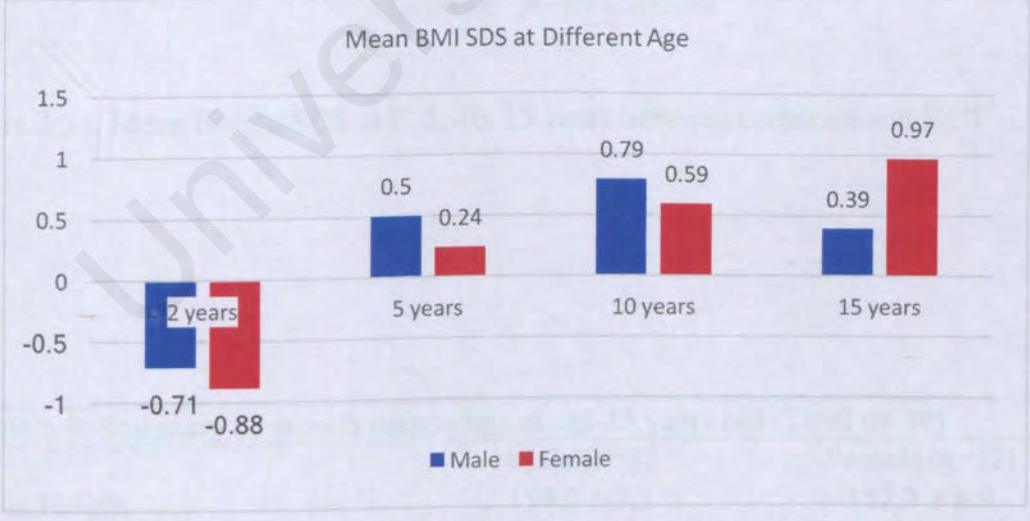

Figure 5.33: Mean BMI SDS at 2, 5, 10 and 15 years

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Nine out of 20 patients were treated with cortisone before converted to Hydrocortisone and 11 patients were treated with Hydrocortisone. Mean height SDS calculated for cortisone group was -0.98 ± 0.9 compared to hydrocortisone -1.1 ± 1.5 cm. Statistically there were no difference noted between this group (Figure 5.34).

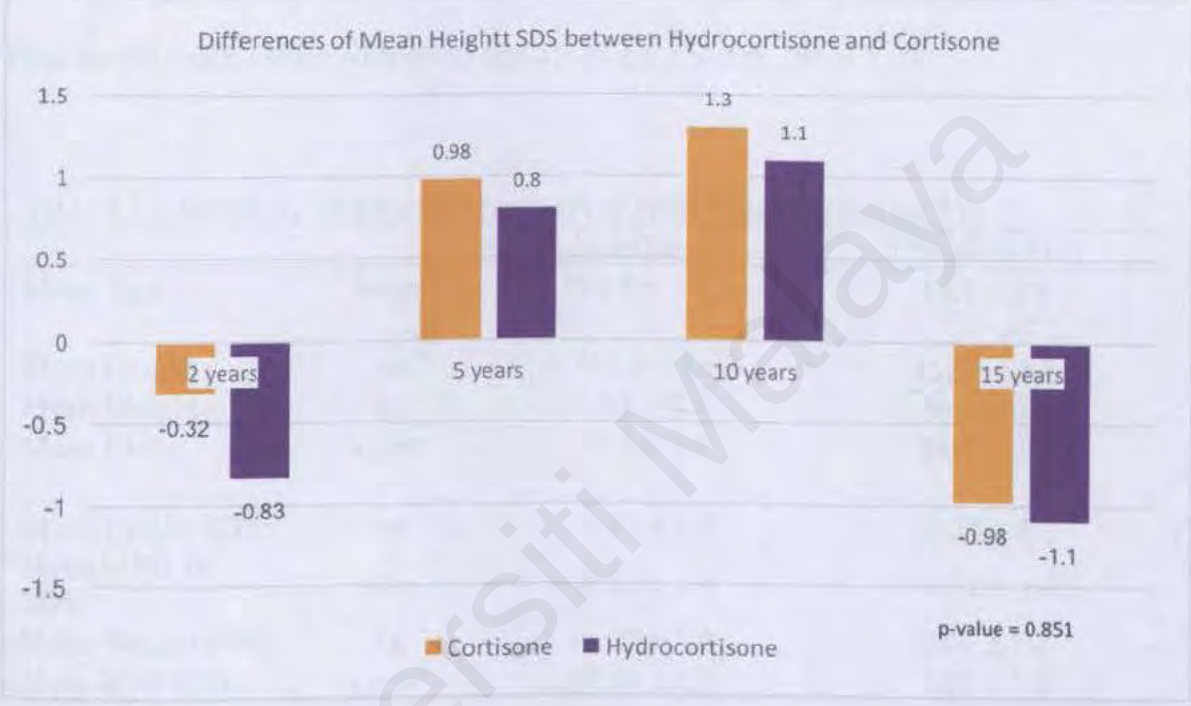

Figure 3.34: Mean Height SDS at 2, 5, 10, 15 years between cortisone and HCT

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Table 5.9: Summary of growth parameters at age 15 years old (Total n= 20)

		Male (n=8)	Female (n=12)
Mean Height	cm	159.9 ± 7.3	152.3 ± 8.9
Mean Weight	kg	53.2 ± 10	53.9 ± 8.5
Mean BMI	kg/m^2	20.7 ± 3.3	23.3 ± 3.6
Mean Height SDS	cm	-0.55 ± 7.3	-1.37 ± 1.5
Mean MPH Ht SDS	cm	-0.02 ± 0.6	-0.75 ±1.6
Mean Weight SDS	kg	-0.22 ± 1.1	0 ± 0.9
Mean BMI SDS	kg/m^2	0.39 ± 1.3	0.97 ± 0.9

5.4.6 Growth of Children with CAH at Final Height

A total of 21patients were followed up until they achieve their final height. Final height is defined as growth velocity less than 1 cm/year, 2 years after menarche or testicular volume of 15-20ml and closed epiphyseal on bone age. Eight out of 21 patients were male with mean age of 17.45 ± 1.5 years at final height. 13 female patients attained final height much earlier with mean age 15.70 ± 1.1 years. *Table 5.10*

Table 5.10: Summary of growth parameters at Final Height (Total n= 21)

		Male (n=8)	Female (n=13)
Mean Age	years	17.5 ± 1.5	15.7 ± 1.1
Mean Height	cm	161.6 ± 10	152.2 ± 8.6
Mean Weight	kg	54.1 ± 9.9	56.1 ± 9.9
Mean BMI	kg/m^2	20.9 ± 2.7	24.7 ± 4.7
Mean Height SDS	cm	-1.63 ± 1.7	-1.29 ± 1.5
Mean MPH Ht SDS	cm	-0.82 ± 1.4	-0.72 ± 1.6
Mean Weight SDS	kg	-1.37 ± 1.5	0.06 ± 1.3
Mean BMI SDS	kg/m^2	-0.08 ± 0.9	1.07 ± 1.1

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The mean height for male was 161.6 ± 10 cm and female was 152.2 ± 8.6 cm. Mean height SDS for both gender was lower in both gender. Male mean height SDS was -1.63 ± 1.7 cm lower than standard population. The mean height SDS for female was -1.29 ± 1.5 cm (Figure 5.35). Mean mid-parental height was -0.82 ± 1.4 cm in male and -0.72 ± 1.6 cm in female (Figure 5.36).

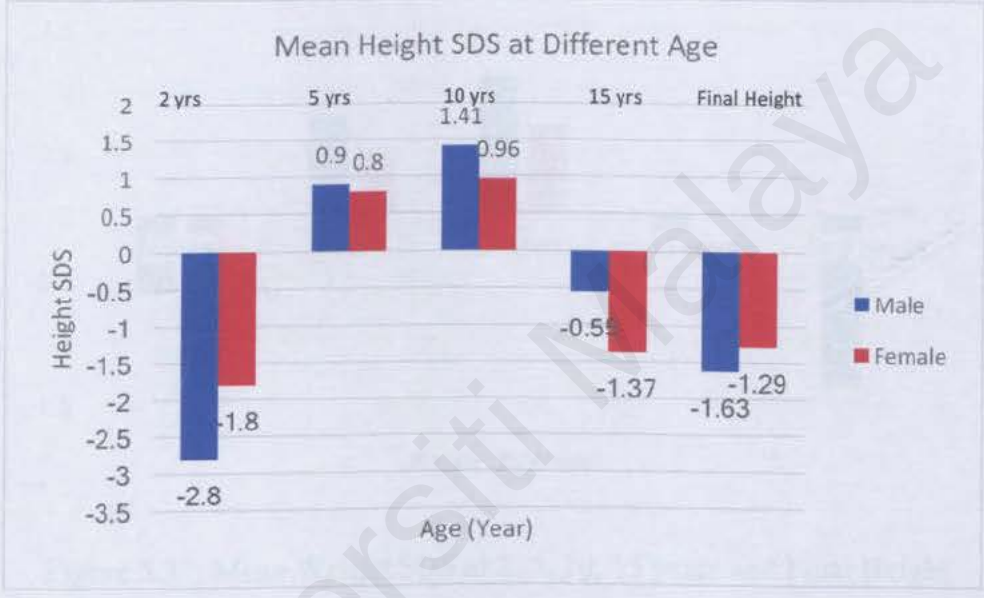

Figure 5.35: Mean Height SDS at 2, 5 ,10, 15 years and Final Height

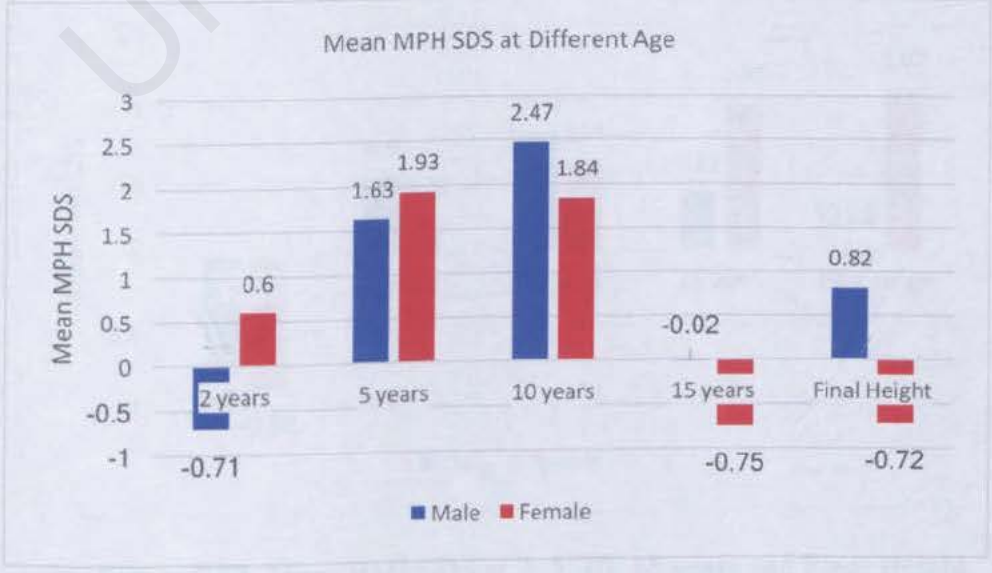

Figure 5.36: Mean MPH SDS at 2, 5, 10, 15 years and Final Height

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At final height, the mean weight was 54.1 ± 9.9 kg in males and 56.1 ± 9.9 kg in females with mean weight SDS -1.37 ± 1.5 kg and -0.72 ± 1.6 respectively (Figure 5.37). The BMI was noted to be increasing in trend for females with mean BMI was 24.7 ± 4.7 kg/m^2 and mean BMI SDS was within overweight range; 1.07 ± 1.1 kg/m^2 (Figure 5.38).

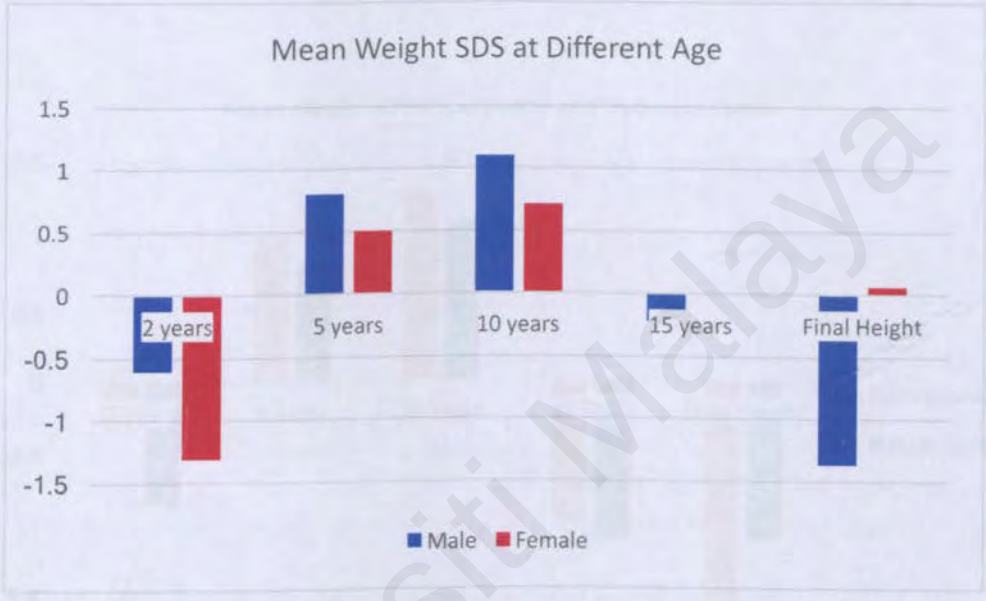

Figure 5.37: Mean Weight SDS at 2, 5, 10, 15 years and Final Height

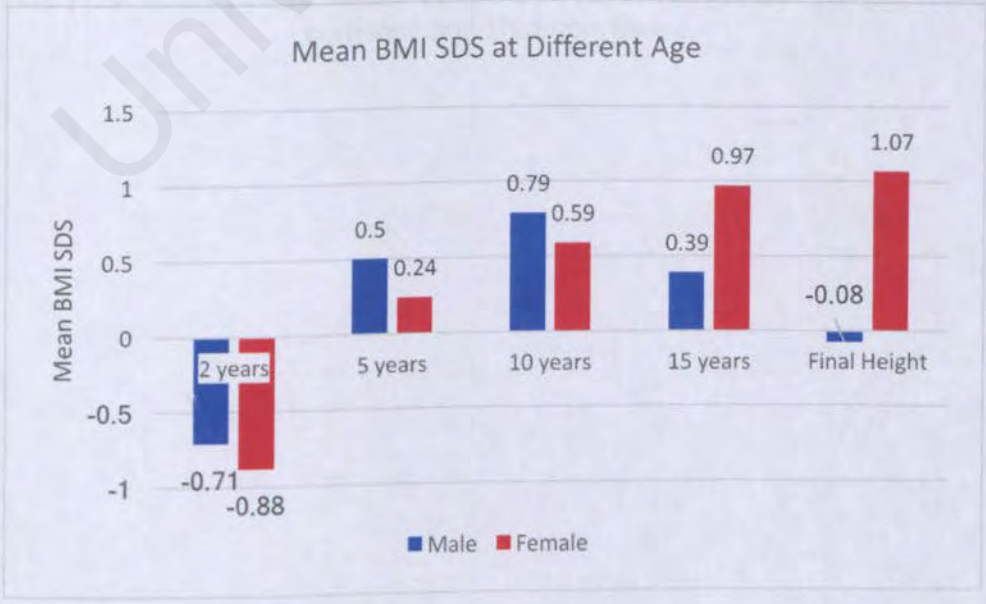

Figure 5.38: Mean BMI SDS at 2, 5, 10, 15 years and Final Height

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Among these 21 patients at final height, 9 patients were treated with cortisone acetate and another 12 patients were treated with hydrocortisone. Mean height SDS was much lower in cortisone group with mean height SDS was -1.82 ± 1.3 cm compared to hydrocortisone group of patients -1.13 ± 1.6 cm. However, it was not proven statistically with p-value of 0.312 (Figure 5.39).

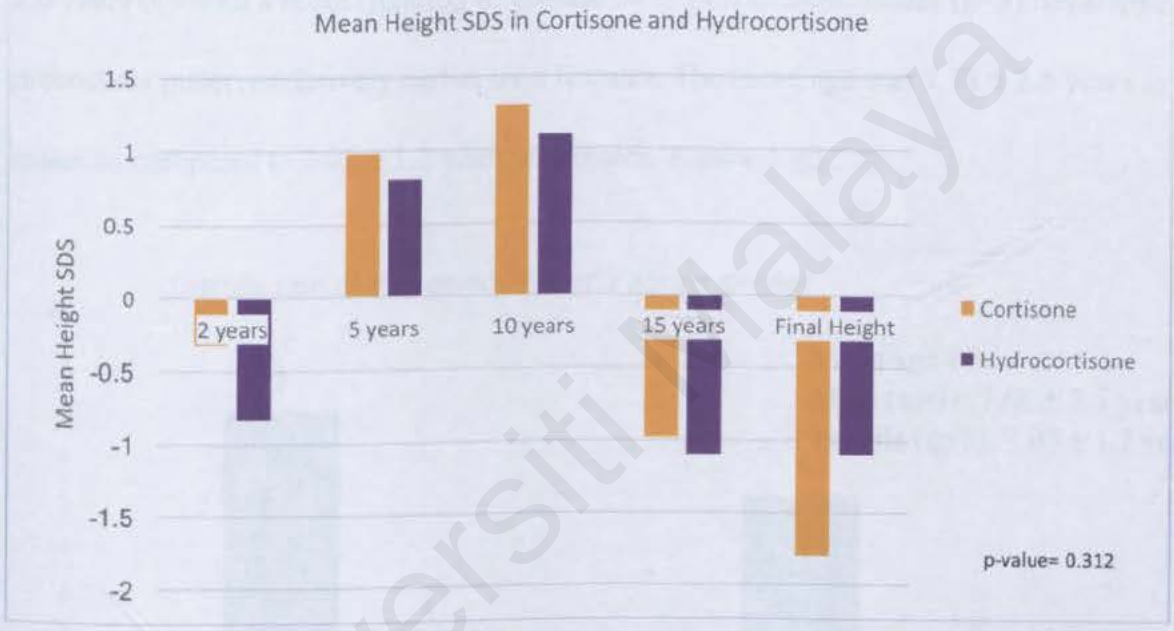

Figure 5.39: Mean Height SDS at 2, 5, 10, 15 years and at Final Height between cortisone and Hydrocortisone

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5.5 COMPLICATION

5.5.1 Precocious Puberty

Amongst the cohort of our patients (n=32), 46.5% (n=15) developed precocious puberty. 80% (12 out of 15) developed central precocious puberty. 58.3% were males (n=7) and 41.7% were females (n=5). 20% developed peripheral precocious puberty (male =1, female= 2). Mean age of patient presented with precocious puberty was 7.4 ± 2.0 years old with a mean duration of disease 74 ± 34.6 months. Males (n=9) developed precocious puberty relatively earlier than females. The mean age was 7.78 ± 2.5 years in males as compared to 7.03 ± 1.2 years in females. *Figure 5.40*

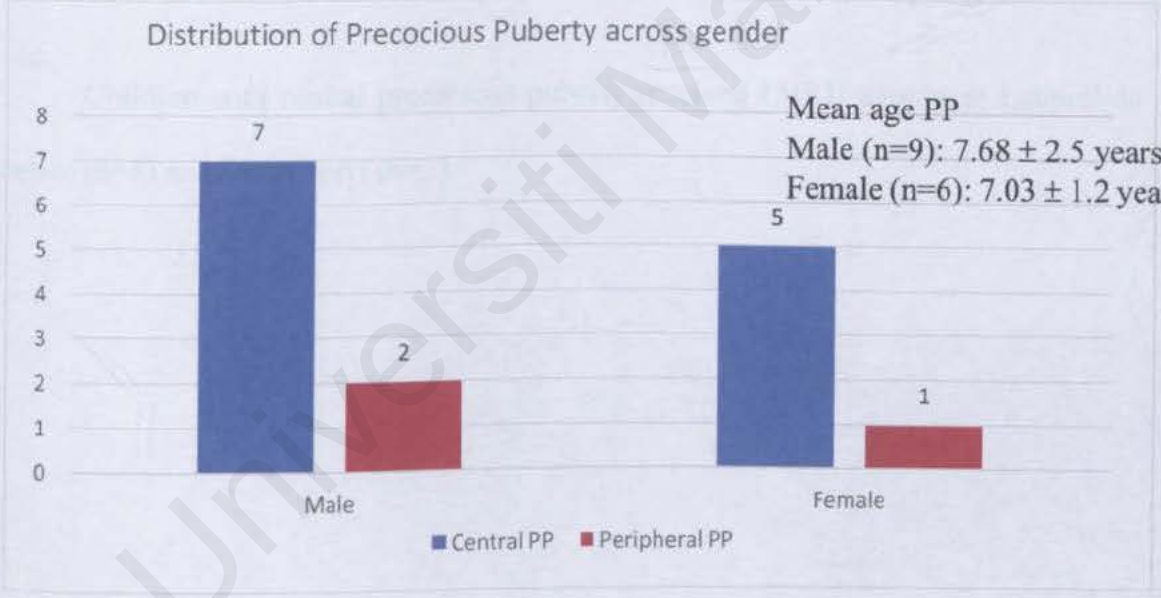

Figure 5.40: Distribution of precocious puberty across gender

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Three children (30%) who had received cortisone acetate and 12 (80%) children treated with hydrocortisone developed precocious puberty. Mean dose for each cortisone and hydrocortisone were 23.5 ± 2.1 mg/m2/day and 15.3 ± 2.8 mg/m2/day. There was no significant association noted between this two group (p= 0.265). All children who had precocious puberty were poor controlled (high serum 17OHP levels). *Table 5.11*

Table 5.11: Development of Precocious Puberty among Cortisone and HCT

	Hydrocortisone	Cortisone acetate
n	12	3
Mean age (years)	7.35 ± 1.9	7.72 ± 3.7
Mean dose glucocorticoids (mg/m2/day)	15.3 ± 2.8	23.5 ± 2.1
Se 17 OHP (nmol/L)	116.2 ± 123	161.5 ± 143 (n=2)

Children with central precocious puberty received LHRH agonist ie Leuprolide acetate (n=8) and Decapeptyl (n=2).

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5.5.2 Adrenal Rest Tumour

Only 1 case developed testicular adrenal rest tumour (TART) out of 32 patients giving prevalence of only 3 % amongst CAH patients seen in paediatric endocrinology. This patient developed TART at age of 11.8 years old and had issues with compliance and poor control. He was on hydrocortisone dose ranging from 15-17 mg/m^2/day. TART was confirmed through imaging of testes (ultrasonography and MRI) and bilateral testicular venous sampling following synacthen stimulation test.

No case of ovarian adrenal rest tumour observed among our female patients.

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5.5.3 Obesity

Majority of our patients fall within normal BMI at all time point. Obesity is defined as BMI SDS more than +2SDS. It was observed that 4 out of 17 of them were obese at age 2 years old, 3 out of 20 patients at 15 years old time point and 4 out of 21 patients at final height (Figure 5.41). It can be multifactorial including nutrition which we did not analyzed. The prevalence of obesity upon completion of final height was 14.2 %.

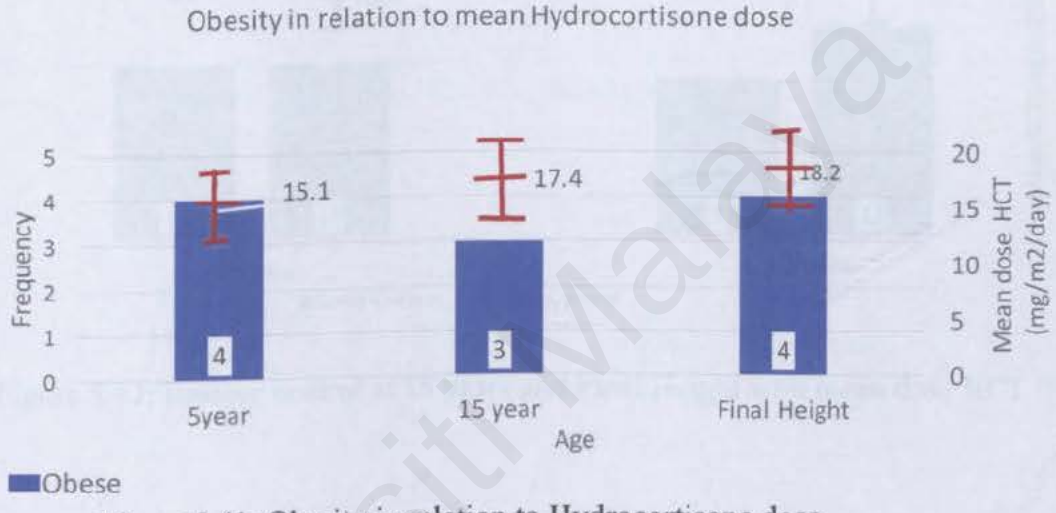

Figure 5.41: Obesity in relation to Hydrocortisone dose

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5.6 Control of Disease

It has been observed from our patients that their disease control was better during early childhood. However, the disease control was poor at age 10 years onwards. Mean dose of hydrocortisone ranging from 13.3 mg/m2/day to 17.6 mg/m2/day.

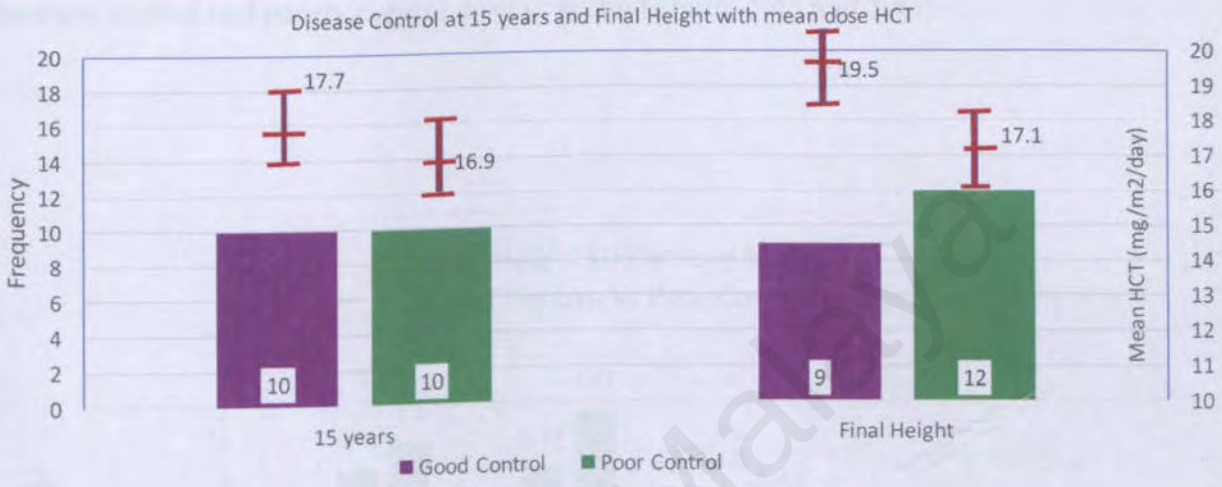

Figure 5.42: Disease control at 15 years and Final Height with mean dose HCT

Table 5.12: Mean Height SDS Differences among Control and Poor Control Disease Group

	Mean Ht SDS			
	5 years (n)	10 years (n)	15 years (n)	Final Height (n)
Male				
Good Control	0.75 ± 0.9 (7)	0.73 ± 0.9 (4)	-0.5 ± 0.5 (4)	-0.99 ± 1.8 (3)
Poor Control	1.30± 2.1 (2)	1.87 ± 0.7 (6)	-0.61 ± 1 (4)	-2.0 ± 1.7 (5)
p-value	0.576	0.058	0.861	0.443
Female				
Good Control	0.86 ± 1.3 (11)	1.17 ±1.5 (6)	-0.66 ± 1.5 (6)	-0.47 ± 1.6 (6)
Poor Control	0.78 ± 0.9 (5)	0.8 ± 0.6 (8)	-2.0 ± 1.0 (6)	-1.99 ±1.0 (7)
	0.909	0.530	0.096	0.058

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We have observed that the mean height SDS was lower in those with poorer control at age 10, 15 and final height for both gender (Table 5.12). The mean height SDS at final height for both gender was lower in poor control disease group. The mean height SDS was higher at age 5 years old despite having poor disease control among males. See Figure 5.42. However, there were no significant difference were seen in mean height SDS between control and poorly control disease group (Figure 5.43 and 5.44)

Figure 5.43: Mean Height SDS among males: Good Control Vs Poor Control

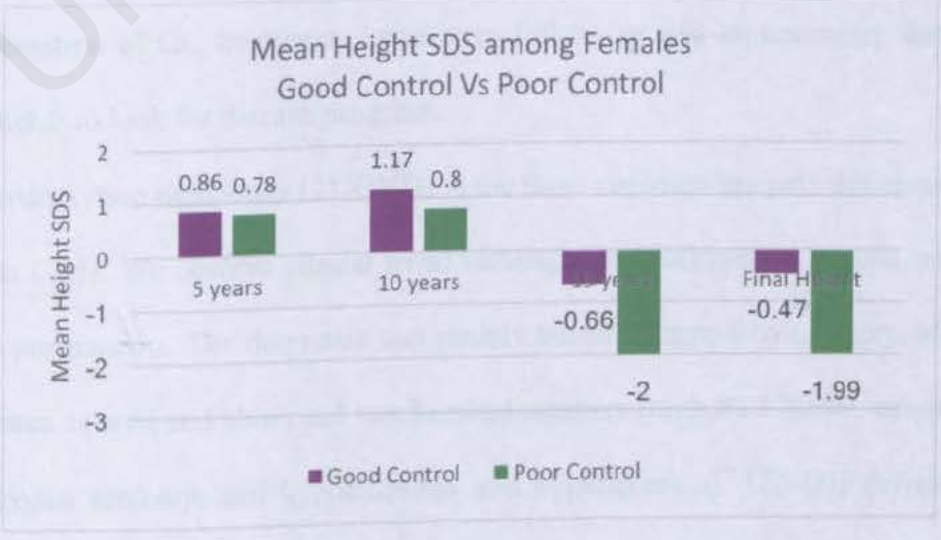

Figure 5.44: Mean Height SDS among females: Good Control Vs Poor Control

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CHAPTER 6: DISCUSSION

6.1 Prevalence of Type of CAH and clinical characteristics.

At present, this would be the first study to look at growth and other associated outcome of children with congenital adrenal hyperplasia (CAH) in Malaysia. However, we were unable to estimate on the prevalence of CAH due to limitation of this study being conducted in a single site tertiary center and with a relatively small sample size.

From this study, we have found that salt wasting CAH is the commonest types of CAH (60.5% n=23) as compared to simple virilizing CAH. There was no non-classical CAH documented amongst our patients. The diagnosis of NC-CAH was most likely under detected as this group of patients may present later in childhood or as young adult with symptoms of hyperandrogenism. We have found a group of children who had temporary/ transient CAH. These children presented with some degree of ambiguous genitalia and had some abnormal biochemical levels. They received glucocorticoid during their early childhood years, however we found that they were on a low dose of hydrocortisone and had completely normal biochemical levels over the years. The diagnosis was revised and Synacthen test was performed. All of these children (n=5) had normal responses. Their serum 17-OHP and testosterone level were low after stimulation test. They remained well following cessation of GC treatment. Long term follow-up will be necessary for this group of patients to look for disease progress.

21-hydroxylase deficiency (21-OHD) is the most common enzyme deficiency in children with CAH. We observe similar trend although no confirmative genetic testing was done in our patients. The diagnosis was mainly based on supportive history, strong clinical features as well and abnormal biochemical markers (high Se 17OHP, excessive adrenal androgen secretion and hyponatremia and hyperkalemia). 11β-OH deficiency accounts for less than 3% of cases involving only one patient who had glucocorticoid

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deficiency, excessive adrenal androgen secretion, hypertension, and hypokalaemia. In this study, we only manage to confirm a genetic diagnosis of 3-β Hydroxylase deficiency CAH in two siblings. Both had adrenal crisis, hyperpigmentation and were undervirilized male.

Distribution of CAH across the ethnicity was equal among the Malays and the Chinese (40% to 39% respectively). This is much representing the distribution of population in this area in Malaysia. We found that the Malays were diagnosed mainly with Salt wasting CAH and the Chinese with Simple Virilizing CAH. It may just be random but, if funds available in the future, it will be interesting to see any genetic preference to certain ethnicity.

As expected in any autosomal recessive disorder, equal gender distribution should be observed. However, in our study population we are seeing more females affected; n=23 (60.5%) and 15 males (39.5%). We suspect that the diagnosis in male children may have been missed and underdiagnosed. The genitalia ambiguity may not be apparent and they may present as sudden death secondary to sepsis or metabolic crisis during neonatal period.

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Majority of our patients (78.9 %) presented early within 6 months of life with mean age 0.76 ± 1.5 years. Those who were diagnosed later presented with pseudo-precocious puberty (PPP) and virilization. As expected all children with Salt Wasting CAH presented early before 6 months. Children with Simple Virilizing CAH presented later and among our cohort of patients, diagnosis of clitoromegaly was missed at birth. *Table 6.1*

Table 6.1: Reason for Clinical Presentation CAH : Khalid et al (onset before 30 days) and Larsson et al (onset before 60 months)

Studies	Reason for Clinical Presentation	Total (%)	Boys N	Girls N
Khalid et al (2014) Great Britain	**Salt Wasting**	27 **(35%)**	15	3
(Onset before 30 days)	**Virilizing of female genitalia**	34 **(44%)**	-	34
	Incomplete masculinization	2 (2.6%)	-	2
	Adrenal insufficiency	3 (3.8%)	2	1
	Affected sibling	11 (14.2%)	5	6
Larsson et al (1990) Sweden	**Salt Wasting** only	47 **(32.9%)**	47	-
(Onset before 60 months)	SW + Virilizing	45 (31.4%)	-	45
	SW + AG	1 (0.7%)	1	-
	Simple Virilizing	50 **(34.9%)**	15	35
	Affected sibling	2 (1.4%)	1	1
UMMC				
Before age 1 year	**SW only**	**12 (31.5%)**	**10**	2
	SW + Virilization	**9 (23.7%)**	1	**8**
	SW + Ambiguous	2 (5.3%)	0	2
	Virilization	4 (10.5%)	2	2
	Ambiguous	2 (5.3%)	0	2
	Hyperpigmentation	1 (2.6%)	0	1
After 1 age	Virilization	8 (21.1%)	2	6

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Laboratory results at diagnosis were as expected for CAH patients. Median level of serum sodium was 126.5 mmol/L and serum potassium was 6.1 mmol/L. These reflect the status of hypoaldosteronism in children with CAH. We also observe high level of Serum 17-OHP at diagnosis with median level of 201.95 nmol/L and Serum testosterone of 7.9 nmol/L. Other hormonal blood parameters as such Aldosterone, ACTH or renin were not sent regularly, hence we do not have enough data for analysis.

Ten patients received treatment with cortisone acetate prior to hydrocortisone once it is available in Malaysia after 1996. Subsequently, all of them were converted to hydrocortisone This is to follow the consensus of Paediatric European CAH guidelines.

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6.2 Growth outcome in Children with CAH

At age 2 years old, their mean height SDS was -0.55 ±1.7 cm for males and -0.73 ± 0.8 cm for females. Their mid parental height SDS was -0.06 ±1.5 cm and -0.60 ± 0.7 cm respectively. Their mean weight SDS and BMI SDS was within the normal range. At 2 years old, nutrition plays an important role to promote normal growth. Comparing to another study done by Bunraungsak (2013), our male children's height SDS were almost similar to their population but different height SDS comparing female children. In a different continent, in Eurasian country; their children with CAH grew better. *Table 6.2*

However, at 5 years old, our CAH children's growth was noted to improve significantly. Their mean height mean SDS at this time point in males were 112.11 ± 6.6 cm and 111.83 ± 5.8 cm in females. Their mean mid-parental height SDS had improved at this point, with mean of 0.87 ± 1.1 in males and 0.83 ± 1.1 in females. The mean weight and BMI was within normal range although four of them were noted to have high BMI SDS > +2SDS consistent suggesting obesity. Improvement of nutrition status could be one of the possible cause for this but data on diet was not available for analysis. The sudden height spurt may suggest precocious pubertal development as analyzed in a different section below.

Similar trend observed at the age of 10 years old, the mean height for each gender was 146 ± 6.4 cm for males and 141.9 ± 6.1 cm for females. Height SDS showed further increment at this age with height SDS in males were 1.41 ± 0.9 cm and 0.96 ± 1.0 cm in females. Nonetheless, our height SDS was shorter compare to study done by Bunraungsak. The mean weight was 39.2 ± 5.9 kg among males and 37.5 ± 4.9 kg in females. The possibilities of pubertal element may play an important role for the height spurt between 5-10 years old.

By 15 years old and at final height review, it has been observed that the height SDS was slowing down. At their final height measurement, the males were shorter with

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mean height of 161.6 ± 10 cm and mean mid-parental height SDS of -1.63 ± 1.7. However, referring to the Malaysian adult height and height SDS population standard reference (which was 164.7 cm and -1.69), their height was comparable (46). The similar trend is observed amongst the females with their mean height of 152.2 ± 8.6 cm as compared to adult Malaysian female of 153.3 cm. [final height SDS was at -1.29 vs -1.54]. Our children with CAH have normal adult height compared to Malaysian population standard. Our mean height SDS was almost the same with the study population in Thailand.

Due to heterogenous treatment given previously; we compared those who were exposed to cortisone acetate and had hydrocortisone only. Similar pattern with mean height SDS were observed. However, at final height SDS, there is a difference seen between this 2 group although no statistical significance was found with p- value of 0.312. This is likely due to the small numbers compared in the 2 groups.

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Table 6.2: Longitudinal Height Data in Various Study

Study (Date)	Type		(n)	FH(cm)	Ht-SDS 2 yrs (n)	Ht-SDS P2 (n)	Ht-SDS FH (n)
Manoli et al (2002) Greece	SW	M	4	170·8 ± 5·6	0·45 ± 0·2 (2)	0·2 ±1·21 (3)	- 0·57 ± 0·8 (4)
		F	13	156·7 ± 6	−0·33 ± 0·9 (8)	0·09 ± 1·3 (11)	-0.61 ± 1 (13)
	SV	M	11	166.1 ± 6.1	1·3 ± 1·4 (2)	1·25 ± 1·5 (6)	-1.05 ± 1 (11)
		F	14	151·6 ± 5·4	1·3 ± 1·6 (5)	0·1 ± 0·6 (10)	-1.4 ± 1 (14)
Bonfig et al (2009) Germany	SW	M	22	-	-	0.1 ±1.2	0.9 ±0.8
		F	32	-	-	0.1 ±1.4	0.7 ± 0.8
	SV	M	13	-	-	1.2 ±1.6	1.3 ±1.0
		F	25	-	-	0.5 ± 1.2	0.9 ± 1.0
Bunraungsak (2013) Thailand	SW	M	14	159.6 ± 3.3	0.60 ± 1.6 (9)	1.73 ± 1.9* (8)	−1.88 ± 0.6 (2)
		F	35	147.9 ± 5.3	−0.32 ± 1.6 (26)	0.19 ± 1.8 (22)	−1.88 ± 1.1 (14)
	SV	M	5	164	- (0)	4.4 ±0.5 (4)	-1.06 (1)
		F	4	149.4 ± 6.9	1.65 ± 0.2 (2)	0.19 ± 0.8 (4)	−1.56 ± 1.4 (2)
UMMC (2017)	SV & SW	M	8	161.6 ± 10	-0.55 ± 1.7 (8)	1.41 ± 0.9* (10)	-1.63 ± 1.7 (8)
		F	13	152.2 ± 8.6	-0.73 ± 0.8 (9)	0.96 ± 1.0* (14)	-1.29 ± 1.5 (13)

P2- puberty Initiation, *- at 10 years age, F- female, M- male

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6.3 Complications

6.3.1 Precocious Puberty

50% of our patient developed precocious puberty (15 out of 32 patients). It means 1 in every 3 children developed central precocious puberty and every 1 in 10 children with CAH developed peripheral precocious puberty. Boys develop puberty earlier as compared to girls. All of our children who developed precocious puberty had poorer disease control prior to development of PP. Adequate glucocorticoid replacement is important to inhibit androgen hypersecretion and to prevent development of central precocious puberty.

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6.3.2 Testicular Adrenal Rest Tumour

Compared with other studies done previously, we report only one out of 32 patients who developed TART giving a prevalence of 3 % in our study population. This rate is much lower compared to other studies worldwide. We may miss cases of TART as we do not have routine ultrasonography screening amongst our patient for surveillance. Screening for TART was proposed to be done at early childhood and annually in peripubertal period in which should be implemented into our center.

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6.3.3 Obesity

One third of our patient developed obesity. Prevalence of obesity was high among our patient at final height 14.2%. Although study from Finkelstein et al support the contribution of glucocorticoid therapy, we were unable to find any association of mean hydrocortisone dose among obese and non- obese group.

Table 6.3: Obesity in various study

Authors	Prevalence		n	Age	Mean BMI SDS	Mean HCT dose ($mg/m^2/day$)
Volk et al (2006) Germany	15/89 (16.8%)	M	41	8.49 ± 5.02	1.03 ± 1.31	15.9 ± 5.36
		F	48	9.18 ± 4.40	0.75 ± 1.37	13.9 ± 3.99
Subbarayan et al (2014)	25/ 106 (23.6%)	-	106	9.2 (range 0.4- 20.5 years)	0 98 (1 42)	13.3
UMMC (1997)	4/21 (14.2%)	M	8	17.5 ± 1.5	-0.08 ± 0.9	19.5 ± 4.2
		F	13	15.7 ± 1.1	1.07 ± 1.1	16.3 ± 4.5

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6.4 Height outcome in association with disease control

We have observed that our patient was shorter in the poorly controlled CAH group with mean SDS at final height -2.0 ± 1.7 in males and -1.99 ±1.0 in females compared to children with good control CAH (-0.99 ± 1.8 in males and -0.47 ± 1.6 in females). However, due to the small sample size, we were unable to show significant difference between the 2 groups.

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CHAPTER 7: CONCLUSION

This retrospective review of patients with congenital adrenal hyperplasia describes demographic as well as types of CAH amongst out patient. Older children with virilization need to be investigated for simple virilizing CAH and non- classical CAH.

Further investigations for central precocious puberty and peripheral precocious puberty need to be done when these children presented with sudden growth spurt as early as 5 years old.

Screening to look for testicular adrenal rest tumour may need to be done routinely and earlier prior to pubertal onset. Following guidelines, ultrasound of the testes should be done yearly to detect abnormalities.

Our study unable to demonstrate higher glucocorticoids dose lead to obesity in children with CAH.

A multicenter study to look for the outcomes and associated complications should be done in future involving other paediatric endocrinology unit under Ministry of Health Hospital would be better. It will also give prevalence of CAH in Malaysia.

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CHAPTER 8: LIMITATIONS

There are several limitations in this study, the list are as follows: -

1. This was a single centre study with low case number. Consequently, the results may not be representative or generalized to other settings.

2. This study was retrospective; therefore, data relied heavily on good documentation. Some important data were lost or incompletely documented hence need to be excluded during point of assessment

3. Compliance, timing, and frequency of glucocorticoid dosing and blood sampling could not be ensured.

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