INTRODUCTION

Congenital Adrenal Hyperplasia (CAH) is an inborn error of metabolism that can produce life-threatening disease in the first one to three weeks of life, unless properly diagnosed and managed. This autosomal recessive disease results in insufficient biosynthesis of cortisol due to an enzyme defect in the adrenal gland. CAH due to 21-hydroxylase deficiency is found in 1/11,000–1/15,000 people in the general population ***(Army, 2010).*** It is classified into three types based on disease severity: classic salt-wasting, classic simple virilizing, and nonclassic ***(Verma et al., 2010).***

CAH can cause virilization/ambiguous genitalia in female infants with the disease and can cause salt-wasting crises in infants of both sexes ***(Dorin et al., 2003)***. Several studies have demonstrated loss of height potency during first year of life ***(Van Der Camp et al., 2002).*** In this period of rapid growth, reduction of growth velocity has considerable effect on final adult height. Whether this decreased height potential is caused by inadequate suppression of adrenal androgens, excess steroid treatment or the salt wasting itself is a matter of debate ***(Savage et al., 2002).*** Current evidence suggests that infancy and peripupertal periods are the time periods where height outcome is most sensitive to glucocorticoids dose **(*Liivak et al., 2009).***

Although the treatment of each child with CAH needs to be individualized, close medical follow-up and laboratory monitoring along with good compliance can often result in positive clinical outcomes. Glucocorticoid excess may result in poor linear growth, weight gain, hypertension, and other unwanted side effects. On the other hand, under treatment results in excess androgen production and advanced skeletal maturation ***(Todd et al., 2010).***

AIM OF WORK

The aim of the work is:

- To analyze growth patterns in 70 children with congenital adrenal hyperplasia diagnosed in the neonatal period in the first year of life.
- To assess the mode of therapy on length.

CONGENITAL ADRENAL HYPERPLASIA

The term congenital adrenal hyperplasia (CAH) refers to a group of autosomal recessive disorders, each of which involves a deficiency of an enzyme involved in the synthesis of cortisol, aldosterone, or both. The clinical manifestations of each form of CAH are related to the degree of cortisol deficiency and/or the degree of aldosterone deficiency. In some cases, these manifestations reflect the accumulation of precursor adrenocortical hormones. When present in supraphysiologic concentrations, these precursors cause abnormalities such as virilization or hypertension ***(Merke et al., 2008)***.

Pathophysiology:

Cortisol is an adrenal steroid hormone that is required for normal endocrine function. Production begins in the second month of fetal life. Poor cortisol production is a hallmark of most forms of CAH. Inefficient cortisol production results in rising levels of ACTH, which in turn induces overgrowth (hyperplasia) and over activity of the steroid-producing cells of the adrenal cortex ***(Speiser et al ., 2010).***

Cortisol deficiency in CAH is usually partial and not the most serious problem for an affected person. Synthesis of cortisol shares steps with synthesis of mineralocorticoids such as aldosterone, androgens such as testosterone, and estrogens

such as estradiol. The resulting excessive or deficient production of these three classes of hormones produces the most important problems for people with CAH. Specific enzyme inefficiencies are associated with characteristic patterns of over- or underproduction of mineralocorticoids or sex steroids ***(Speiser et al., 2010).***

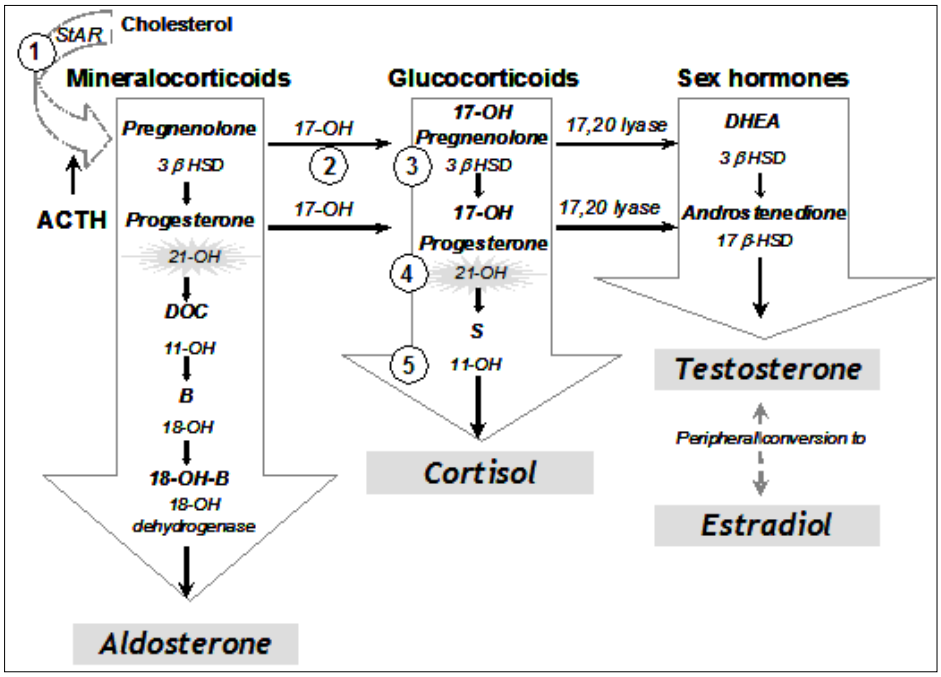

Figure 1: Illustrates adrenal steroidogenesis: Five enzymatic steps necessary for cortisol production are shown in numbers. 1= 20, 22 desmolase, 2= 17 hydroxylase (17-OH), 3=3ß-hydroxysteroid dehydrogenase (3ß HSD), 4=21 hydroxylase (21-OHD), 5=11ß hydroxylase (11-OH) In the first step of adrenal stereoidgeneis, cholesterol enters mitochondria via a carrier protein called StAR. ACTH stimulates cholesterol cleavage, the rate limiting step of adrenal steroidogenesis *(Goto et al., 2006).*

Adrenal steroidogenesis occurs in three major pathways: glucocorticoids, mineralocorticoids, and sex steroids as shown in Figure 1. These take place in different areas of the adrenal cortex: glucocorticoids (particularly cortisol), androgens, and estrogens in the zona fasciculata and reticularis; and aldosterone in the zona glomerulosa. These pathways serve as the basis for understanding the different forms of CAH. ACTH regulates adrenal steroid production via a rate-limiting step that results in pregnenolone, the principal substrate for the steroidogenic pathway. It promotes Steroid acute regulatory protein (StAR) function in transporting free cholesterol to the inner mitochondrial membrane, the site where a side chain cleavage occurs and the first step in steroidogenesis takes place ***(Goto et al., 2006).***

The central nervous system controls the secretion of ACTH, its diurnal variation, and its increase during periods of physiological stress via the corticotropin-releasing factor (CRF) produced by the hypothalamus. The hypothalamic-pituitary-adrenal feedback system is mediated through the circulating level of plasma cortisol by negative feedback of cortisol on CRF and ACTH secretion. Therefore, any CAH condition that results in a decrease in cortisol secretion leads to increased ACTH production, which in turn stimulates (1) excessive synthesis of adrenal products in those pathways unimpaired by the enzyme deficiency and (2) a build-up of

precursor molecules in pathways blocked by the enzyme deficiency ***(Goto et al., 2006).***

The clinical symptoms of the five different forms of CAH result from the particular hormones that are deficient and those that are produced in excess In the most common form (21 OHD-CAH), the function of 21-hydroxylating cytochrome 450 is inadequate, creating a block in cortisol production pathway. This leads to an accumulation of 17-hydroxyprogesterone (17-OHP), a precursor adjacent to the 21-hydroxylation step. Excess 17-OHP is then shunted into the intact androgen pathway to form 4-androstenedione. Mineralo-corticoid deficiency is a feature of the most severe form of the disease called salt wasting CAH. The enzyme defect in the non-classical form of 21-OHD CAH is only partial and salt wasting in this mild form of the disease is not evident ***(Goto et al., 2006).***

Forms of CAH:

1. 21-Hydroxylase Deficiency:

- ***Salt-wasting 21-hydroxylase deficiency (SW-CAH):***

When the loss of 21-hydroxylase function is severe, adrenal aldosterone secretion is not sufficient for sodium reabsorption by the distal renal tubules, and individuals suffer from salt wasting as well as cortisol deficiency and androgen

excess. The salt wasting is presumed to result from inadequate secretion of salt-retaining steroids, primarily aldosterone. In addition, hormonal precursors of the 21-OH enzyme may act as antagonists to mineralocorticoid action in the sodium-conserving mechanism of the immature newborn renal tubule ***(Sugino et al., 2006).***

- ***Simple-virilizing 21-hydroxylase deficiency:***

Diagnosis at birth of a female with simple virilizing CAH is usually made immediately because of the apparent genital ambiguity with no salt losing symptoms. Since the external genitalia are not affected in newborn males, hyper pigmentation may be the only clue suggesting increased ACTH secretion and cortisol deficiency. Diagnosis at birth in males thus rests on prenatal or newborn screening ***(Wajnrajch et al., 2010).***

- ***Non-classical 21-hydroxylase deficiency:***

Non-classical 21-OHD (NC 21-OHD), previously known as late-onset 21-OHD, is much more common than the classical form. Individuals with the non-classical (NC) form of 21-OHD have only mild to moderate enzyme deficiency and present postnatally, eventually developing signs of hyper androgenism. Females with NC-CAH do not have virilized genitalia at birth. NC-CAH may present at any age after birth with a variety of hyper androgenic symptoms. This form of CAH results from a

mild deficiency of the 21-hydroxylase enzyme. Table (1) summarizes main clinical characteristics of all forms of 21 OHD CAH. While serum cortisol concentration is typically low in patients with the classic form of the disease, it is usually normal in patients with NC 21-OHD ***(Oksana et al., 2010).***

Table 1: Clinical Features in Individuals with Classic and Nonclassic 21-Hydroxylase Deficiency in the Untreated Form ***(Oksana et al., 2010).***

Feature	**21-OH Deficiency**	
	Classic	**Nonclassic**
Prenatal virilization	Present in females	Absent
Postnatal virilization	Males and females	Variable
Salt wasting	~75% of all individuals	Absent

2. 11-β Hydroxylase Deficiency:

Virilization and low renin hypertension are the prominent clinical features of 11β hydroxylase deficiency (11β-OHD) ***(Nimkarn et al., 2008).*** The virilizing signs and symptoms of this disorder are similar to classical 21-OHD. Despite failure of aldosterone production, overproduction of DOC, in vivo a less potent mineralocorticoid, causes salt retention and hypertension ***(Mimouni et al., 1995).***

In addition, hypertension correlates variably with biochemical values, and clinical signs of mineralo-cortiocid excess and the degree of virilization are not well correlated. Some severely virilized females are normotensive, whereas mildly virilized patients may experience severe hypertension leading to fatal vascular accidents ***(Globerman et al., 1998).*** Complications of long standing uncontrolled hypertension, including cardiomyopathy, retinal vein occlusion and blindness have been reported in 11β-OHD patients. Potassium depletion develops concomitantly with sodium retention, but hypokalemia is variable. Renin production is suppressed secondary to mineralo-cortiocid-induced sodium retention and volume expansion. Aldosterone production is low secondary to low serum potassium and low plasma renin ***(Joehrer et al., 1997).***

3. 3-β Hydroxysteroid Dehydrogenase Deficiency:

There are two forms of the 3*β*-hydroxysteroid dehydrogenase enzyme (3*β*-HSD): type I and type II. Type II 3*β*-HSD enzyme is expressed in the adrenal cortex and gonads and is responsible for conversion of Δ5 (delta 5) to Δ4 (delta 4) steroids. This enzyme is essential for the formation of progesterone, which is the precursor for aldosterone, and 17-OHP, which is the precursor for cortisol in the adrenal cortex as well as for androstenedione, testosterone, and estrogen in the

adrenal cortex and gonads. Thus, genital ambiguity can result in both sexes ***(Pang et al., 2001)*.**

4. 17α-Hydroxylase/17,20 Lyase Deficiency:

Steroid 17α-hydroxylase/17,20 lyase deficiency accounts for approximately 1% of all CAH cases and affects steroid synthesis in both the adrenals and gonads. Patients have impaired cortisol synthesis, leading to ACTH oversecretion, which increases serum levels of deoxycorticosterone and especially corticosterone. 17α-Hydroxylase/17, 20 lyase deficiency is often recognized at puberty in female patients who fail to develop secondary sex characteristics& may develop hypertention in early life ***(Miller et al., 1997).***

5. Congenital Lipoid Adrenal Hyperplasia:

Congenital lipoid adrenal hyperplasia is an extremely rare and severe form of CAH which is caused by mutations in the (StAR) protein. Both the adrenal glands and the gonads exhibit a severe defect in the conversion of cholesterol to pregnenolone ***(Bose et al., 2007)***. More specifically, StAR mediates the acute steroidogenic response by moving cholesterol from the outer to inner mitochondrial membrane (the rate-limiting step of steroidogenesis), and when this does not occur, cholesterol and cholesterol esters accumulate ***(Miller et al., 2000).***

More recently, several cases have been reported that demonstrate that lipoid CAH has a spectrum of clinical

presentation, with varying degrees of genital ambiguity (including normal male genitalia in a 46, XY male) and adrenal insufficiency. Mutations in the StAR protein have been reported that retain partial protein function, leading to variable phenotype ***(Sahakitrungruang et al., 2010)***

6. Cytochrome 450 Oxidoreductase Deficiency:

The official name of this gene is "P450 (cytochrome) oxidoreductase". The *POR* gene provides instructions for making the enzyme cytochrome P450 oxidoreductase. This enzyme is required for the normal functioning of more than 50 enzymes in the cytochrome P450 family. Cytochrome P450 enzymes are involved in the formation of steroid hormones as testosterone, estrogen, corticosteroids and aldosterone. Additionally, cytochrome P450 enzymes are involved in the metabolism of ingested substances, such as medications, in the liver ***(Arlt et al., 2004)***.

Cytochrome P450 oxioreductase deficiency is another rare form of CAH that is caused by 24mutations in the *POR* gene. The 17-OH progesterone levels are elevated, as in 21-hydroxylase deficiency, while androgen levels are low; cortisol may be normal but is poorly responsive to adrenocorticotropic hormone. Most patients also have a constellation of skeletal malformations, termed Antley-Bixler syndrome, which includes craniosynostosis, radio-ulnar synostosis, midface hypoplasia and bowed femurs ***(Scott et al., 2008)***.

Table 2: Types of CAH, enzymatic defects, genetic errors & their effects on adrenal hormones ***(Vos et al., 2010).***

Common medical term	%	Enzyme(s)	Locus	Substrate(s)	Product(s)	Mineralo-corticoids	Androgens
21-hydroxylase CAH	90-95%	P450c21	6p21.3	17OH-progesterone→ progesterone→	11-deoxycortisol DOC	↓	↑
11β-hydroxylase CAH	5%	P450c11β	8q21-22	11-deoxycortisol→ DOC→	cortisol corticosterone	↑	↑
3β-HSD CAH	very rare	3βHSD II	1p13	pregnenolone→ 17OH-pregnenolone→ DHEA→	progesterone 17OH-progesterone androstenedione	↓	↓
17α-hydroxylase CAH	very rare	P450c17	10q24.3	pregnenolone→ progesterone→ 17OH-pregnenolone→	17OH-pregnenolone 17OH-progesterone DHEA	↑	↓
lipoid CAH (20,22-desmolase)	very rare	StAR P450scc	8p11.2 15q23-q24	transport of cholesterol cholesterol→	into mitochondria pregnenolone	↓	↓

Epidemiology:

Frequency: Data from close to 6.5 million newborn screenings worldwide indicate that classical CAH occurs in 1:13,000 to 1:15,000 live births ,with a prevalence as high as 1/750 people in some populations such as the Yupik Eskimos in Alaska and the people of La Réunion in France... It is estimated that 75% of patients have the salt-wasting phenotype ***(Wajnrajch et al., 2010).*** CAH caused by 21-hydroxylase deficiency is found in all populations. 11-beta-hydroxylase deficiency is more common in persons of Moroccan or Iranian-Jewish descent ***(Bongiovanni et al., 1993).***

Race: CAH occurs among people of all races. Congenital adrenal hyperplasia secondary to CYP21A1 mutations and deletions is particularly common among the Yupik Eskimos ***(Bongiovanni et al., 1993).***

Sex:

Because all forms of CAH are autosomal recessive disorders, both sexes are affected with equal frequency. However, because accumulated precursor hormones or associated impaired testosterone synthesis impacts sexual differentiation, the phenotypic consequences of mutations or deletions of a particular gene differ between the sexes ***(Bongiovanni et al., 1993).***

Age:

Classic congenital adrenal hyperplasia is generally recognized at birth or in early childhood because of ambiguous genitalia, salt wasting, or early virilization. Nonclassic adrenal hyperplasia is generally recognized at or after puberty because of oligomenorrhea or virilizing signs in females ***(Bongiovanni et al., 1993).***

Clinical Presentation:

The symptoms of CAH vary depending upon the form of CAH and the gender of the patient. Symptoms can include:

(A) Clinical presentation in females

- Females with severe forms of adrenal hyperplasia due to deficiencies of 21-hydroxylase, 11-beta-hydroxylase or 3-beta-hydroxysteroid dehydrogenase have ambiguous genitalia at birth due to excess adrenal androgen production in utero **(Fig. .2)** ***(Speiser et al ., 2010).***

- Mild forms of 21-hydroxylase deficiency or 3βHSD deficiency in females are identified later in childhood because of precocious pubic hair, clitoromegaly, or both, often accompanied by accelerated growth and skeletal maturation due to excess postnatal exposure to adrenal androgens (Fig. 3 & 4) ***(New et al., 1997)***.