



# **The Relation between Echocardiographic Features and Androgen Profile in Newly Diagnosed Patients with Congenital Adrenal Hyperplasia**

*Thesis*

Submitted for partial fulfillment of Master Degree  
in Pediatrics

*By*

**Mai Mahmoud Mahmed Ahmed**

M.B.,B.Ch (2010), Faculty of Medicine, Ain-Shams University

*Under Supervision of*

**Prof. Dr. Heba Hassan Elsedfy**

Professor of Pediatrics

Faculty of Medicine, Ain-Shams University

**Dr. Omneya Ibrahim Youssef**

Assistant Professor of Pediatrics

Faculty of Medicine, Ain-Shams University

**Dr. Tarek Mostafa Kamal**

Consultant of Human Genetics

Faculty of Medicine, Ain-Shams University

**Faculty of Medicine  
Ain-Shams University  
2017**

## Abstract

**Introduction:** Congenital adrenal hyperplasia (CAH) encompasses a group of inherited autosomal recessive diseases affecting adrenal steroid synthesis. The impaired cortisol secretion causes ACTH levels to rise and stimulate adrenocortical hormone secretion, resulting in adrenal hyperplasia, and increased production.

**Aim of the Work:** To evaluate echo-cardio graphic functions in infants with congenital adrenal hyperplasia at baseline before starting glucocorticoid therapy.

**Patients and Methods:** This is a prospective case-control study that included thirteen patients diagnosed as having congenital adrenal hyperplasia and are following-up regularly at the Pediatric Endocrinology Clinic Children Hospital, Ain-Shams University during the period from November 2014 to April 2016.

**Results:** This case-control study was conducted on thirteen congenital adrenal hyperplasia pediatric patients due to 21-OHase deficiency. All patients were diagnosed based on clinical and laboratory basis and are following-up regularly at the Pediatric Endocrinology Clinic, Children's Hospital, Ain-Shams University.

They included 8(61.5%) females (46 XX) and 5 (38.5%) males (46XY), their ages ranged between 0.05 –0.7years, with a median (IQR) of 0.14 (0.08 – 0.35) years. Patients were compared with 13 healthy age- and sex-matched controls for evaluation of echocardiographic measurements.

**Conclusion:** Blood pressure levels are substantially low in CAH patients at base line before starting glucocorticoid therapy. Patients with classical CAH had an increased risk for developing myocardial dysfunction and subclinical atherosclerosis.

**Recommendations:** Measuring blood pressure regularly with a careful anthropometric examination in the clinical setting for patients with congenital adrenal hyperplasia (CAH) are mandatory points for good control of these patients.

---

**Keywords:** Echocardiographic, Androgen Profile, Newly Diagnosed, Congenital Adrenal Hyperplasia



## ACKNOWLEDGEMENT

First of all, thanks to **Allah** whose magnificent help was the main factor in completing this work.

No words can express my deep sincere feelings Towards **Prof. Dr. Heba Hassan Elsedfy**, Professor of Pediatrics, Faculty of Medicine-Ain Shams University for her continuous encouragement, guidance and support she gave me throughout the whole work. It has been a great honor for me to work under her generous supervision.

I would like to express my deepest appreciation, respect and thanks to **Dr. Omneya Ibrahim Youssef**, Assistant Professor of Pediatrics, Faculty of Medicine-Ain Shams University, for her continuous guide in all aspects of life beside his great science, knowledge and information.

I would like to express my deepest appreciation, respect and thanks to **Dr. Tarek Mostafa Kamal**, Consultant of Human Genetics, Faculty of Medicine-Ain Shams University, for his continuous guide in all aspects of life beside his great science, knowledge and information.

Last but not least, sincere gratitude to ***My Family*** for their continuous encouragement and spiritual support.

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

سببنا انك لا تعلم لنا  
إلا ما علمتنا إنك أنت  
العليم العظيم

صدق الله العظيم

سورة البقرة الآية: ٣٢

# Contents

Subjects	Page
List of abbreviations.....	II
List of figures.....	VI
List of tables.....	VIII
• <b>Introduction</b> .....	1
• <b>Aim of the work</b> .....	4
• <b>Review of Literature</b>	
♦ <b>Chapter (1):</b> Congenital Adrenal Hyperplasia.....	5
♦ <b>Chapter (2):</b> Effect of Steroid on Cardiovascular System in patients with Congenital Adrenal Hyperplasia.....	35
• <b>Patients and Methods</b> .....	59
• <b>Results</b> .....	76
• <b>Discussion</b> .....	103
• <b>Summary</b> .....	117
• <b>Conclusion</b> .....	120
• <b>Recommendations</b> .....	121
• <b>References</b> .....	123
• <b>Appendices</b> .....	156
• <b>Arabic Summary</b>	

## **List of Abbreviations**

$\Delta 4A$	: Androstenedione
11BOHD	: 11B hydroxylase deficiency
17B-HSD	: 17B hydroxy steroid dehydrogenase
17OHP	: 17-hydroxyprogesterone
17OHPreg	: 17-hydroxypregnenolone
3BHSD	: 3B hydroxy steroid dehydrogenase
3BHSDD	: 3B hydroxy steroid dehydrogenase deficiency
ACTH	: Adrenocorticotrophic hormone
BCIP	: 5-bromo-4-chloro-3-indolyl phosphate
BMI	: Body mass index
BP	: Blood pressure
BSA	: Body surface area
CAH	: Congenital adrenal hyperplasia
CA-IMT	: Carotid artery intima media thickness
CCD	: Common collecting duct
CECs	: Circulating endothelial cells
CVD	: Cardiovascular disease
DBP	: Diastolic blood pressure
DcT	: Deceleration time
DHEA	: Dehydroepiandrosterone

## *List of Abbreviations*

---

DHT	: Dihydrotestosterone
DNA	: Deoxyribonucleic acid
DOC	: Deoxycorticosterone
DSD	: Disorder of sex development
EP	: Epinephrine
ET	: Ejection time
FS	: Fractional shortening
GCS	: Glucocorticoids
GR	: Glucocorticoid receptors
HOMA	: Homeostasis model assessment
HSBB1	: 3B hydroxy steroid dehydrogenase B1 gene
HSBB2	: 3B hydroxyl steroid dehydrogenase B2 gene
hs-CRP	: High sensitive c-reactive protein
IL-6	: Interleukin-6
IM	: Intramuscular
IV	: Intravenous
IV	: Interventricular
IVCT	: Isovolumic ventricular contraction time
IVRT	: Isovolumic ventricular relaxation time
IVST	: Interventricular septal thickness during diastole
K+	: Potassium ions
LDL	: Low density lipoprotein

## *List of Abbreviations*

---

LV	: Left ventricle
LVESd	: Left ventricular end systolic diameter.
LVM	: Left ventricular mass
LVMi	: Left ventricular mass index
LVPWT	: Left ventricular posterior wall thickness during diastole
LVWT	: Left ventricular wall thickness
M- mode	: Motion-mode
MCS	: Mineralocorticoids.
MPI	: Myocardial performance index
MR	: Mineralocorticoid receptors
Na <sup>+</sup>	: Sodium ions
NBT	: Nitro blue tetrazolium
NC	: Non classical
NE	: Nor-epinephrin
NO	: Nitric oxide
ORD	: p450 oxidoreductase deficiency
PCR	: Polymerase chain reaction
PNMT	: Phenylethanolamine N-methyltransferase
PRA	: Plasma renin activity
RV	: Right ventricle
SBP	: Systolic blood pressure
SDS	: Standard deviation scores



## *List of Abbreviations*

---

SV	: Simple virilizing
SW	: Salt wasting
T	: Testosterone
TART	: Testicular adrenal rest tumors
TDI	: Tissue Doppler imaging
THB	: Tetrahydro-corticosterone.
THDOC	: Tetrahydro-deoxycorticosterone
THS	: Tetrahydrodeoxycortisol
TNF- $\alpha$	: Tumor necrosis factor alpha
UGS	: Urogenital sinus

## **List of Figures**

<b><u>No.</u></b>	<b><u>Figure</u></b>	<b><u>Page</u></b>
<b><u>1</u></b>	Regulation of cortisol secretion in normal subjects and in patients with congenital adrenal hyperplasia.	<b>7</b>
<b><u>2</u></b>	Abnormal adrenal steroid biosynthesis in 21-hydroxylase.	<b>8</b>
<b><u>3</u></b>	A Boy with salt-losing CAH present at 7–10 days of age with a salt losing adrenal crisis; some have hyperpigmentation on physical examination.	<b>11</b>
<b><u>4</u></b>	Clinical presentation of classic 21-hydroxylase deficiency.	<b>12</b>
<b><u>5</u></b>	Different degrees of virilization according to the scale developed by Prader.	<b>13</b>
<b><u>6</u></b>	The common, mutations in CYP21, their corresponding clinical disease presentations, and their residual activities were assayed after expression of recombinant enzyme in vitro.	<b>16</b>
<b><u>7</u></b>	Short stature in a male patient with congenital adrenal hyperplasia secondary to 21-hydroxylase deficiency.	<b>25</b>
<b><u>8</u></b>	Transitional care of patients with CAH.	<b>32</b>
<b><u>9</u></b>	Steroidogenic pathway.	<b>36</b>
<b><u>10</u></b>	Glucocorticoid and mineralocorticoid receptors as transcription factors.	<b>37</b>
<b><u>11</u></b>	Consequences of C-21 hydroxylase deficiency.	<b>41</b>
<b><u>12</u></b>	Measuring infant length.	<b>61</b>
<b><u>13</u></b>	Illustration showing the sites where the measurements of the diastolic diameter of the right ventricle/RVDd.	<b>65</b>
<b><u>14</u></b>	The Mitral Inflow Velocity Profile.	<b>66</b>

## *List of Figures*

---

<b><u>No.</u></b>	<b><u>Figure</u></b>	<b><u>Page</u></b>
<b><u>15</u></b>	Tissue Doppler imaging.	<b>68</b>
<b><u>16</u></b>	Comparison between systolic blood pressure SD between patients and controls.	<b>87</b>
<b><u>17</u></b>	Comparison between diastolic blood pressure SD between patients and controls.	<b>87</b>
<b><u>18</u></b>	Comparison between systolic blood pressure, diastolic blood pressure and heart rate between patients and controls.	<b>88</b>
<b><u>19</u></b>	Comparison between M mode parameters between patients and controls.	<b>90</b>
<b><u>20</u></b>	Comparison of diastolic function parameter between patients and controls.	<b>92</b>
<b><u>21</u></b>	Comparison between tissue doppler parameters in patients and controls.	<b>94</b>
<b><u>22</u></b>	Comparison of myocardial performance index & CIMT between patients and controls.	<b>96</b>
<b><u>23</u></b>	Correlation between 17OH-P (ng/ml) and LVPWT (mm).	<b>99</b>
<b><u>24</u></b>	Correlation between 17OH-P(ng/ml) and St (cm/s).	<b>99</b>
<b><u>25</u></b>	Correlation between DHEA (ng/ml) and FS%.	<b>102</b>

## **List of Tables**

<b><u>No.</u></b>	<b><u>Table</u></b>	<b><u>Page</u></b>
<b><u>1</u></b>	Features of each enzyme defect in CAH.	<b>21</b>
<b><u>2</u></b>	Diagnostic marker steroids characteristically increased in the different CAH variants.	<b>22</b>
<b><u>3</u></b>	Prader classification.	<b>62</b>
<b><u>4</u></b>	Demographic data of patients.	<b>77</b>
<b><u>5</u></b>	Clinical and auxological data of patients.	<b>78</b>
<b><u>6</u></b>	Laboratory data at diagnosis of patients.	<b>79</b>
<b><u>7</u></b>	Systolic function of the studied patients by M mode.	<b>80</b>
<b><u>8</u></b>	Diastolic functions of patients by pulsed Doppler.	<b>81</b>
<b><u>9</u></b>	Tissue Doppler parameters of patients.	<b>82</b>
<b><u>10</u></b>	Myocardial performance index & Carotid artery intima media thickness of patients.	<b>83</b>
<b><u>11</u></b>	Genotyping of patients.	<b>84</b>
<b><u>12</u></b>	Comparison of anthropometric measurements between patients and controls.	<b>85</b>
<b><u>13</u></b>	Comparison between the blood pressure & heart rate in patients & controls.	<b>86</b>
<b><u>14</u></b>	Comparison between systolic function by M mode of both patients & controls.	<b>89</b>
<b><u>15</u></b>	Diastolic functions in patients & controls.	<b>91</b>
<b><u>16</u></b>	Tissue Doppler parameters in patients & controls.	<b>93</b>
<b><u>17</u></b>	Myocardial performance index & Carotid artery intima media thickness in patients & controls.	<b>95</b>

## *List of Figures*

---

<b><u>No.</u></b>	<b><u>Table</u></b>	<b><u>Page</u></b>
<b><u>18</u></b>	Correlation between delta-4 androstendione, 17-OH progesterone and Echo parameters in patients.	<b>97</b>
<b><u>19</u></b>	Correlation between free, total Testosterone level and Echo parameters in patients.	<b>100</b>
<b><u>20</u></b>	Correlation between DHEA and Echo parameters in patients.	<b>101</b>

## Introduction

Congenital adrenal hyperplasia (CAH) encompasses a group of inherited autosomal recessive diseases affecting adrenal steroid synthesis (*White and Speiser, 2000*).

The impaired cortisol secretion causes ACTH levels to rise and stimulate adrenocortical hormone secretion, resulting in adrenal hyperplasia, and increased production of androgens and steroid precursors before the enzymatic defect (*Forest et al., 2005*).

The most frequent CAH variant, accounting for 95% of all affected patients, is 21- hydroxylase deficiency and caused by inactivating mutations in the 21- hydroxylase gene (P450c21) which is designated (CYP21) (*White and Speiser, 2000*). Deficiency in P450c21 activity prevents the conversion of 17-hydroxyprogesterone to 11-deoxycorticosterone. Most patients are compound heterozygotes having different mutations of the CYP21 gene on each allele (*Hsien-Hsiung et al., 1996*).

Two distinct phenotypes are recognized in CAH due to 21-OHD: Classical CAH, the most severe form comprises both salt- wasting (SW) and simple virilizing

(SV) forms, with a worldwide incidence of 1:15000 livebirths, and the Non-classical (NC) form which may be asymptomatic or associated with signs of postnatal or even adult onset androgen excess (*Forest et al., 2005*).

Treatment of CAH consists of gluco-corticoids (GCs) and, when necessary, mineralocorticoids to prevent adrenal crisis and to suppress the abnormal secretion of androgens and steroid precursors from the adrenal cortex (*Oglivie et al., 2006*). Lifelong glucocorticoid replacement therapy is often required in CAH patients to reduce adrenal androgen excess (*King et al., 2006*).

The therapeutic spectrum of glucocorticoids is narrow and supraphysiological doses are often needed to control the hyperandrogenism (*Arlt et al., 2010*). It has been suggested that patients with CAH develop unfavourable cardiovascular risk profile either because of the hyperandrogenism in untreated or undertreated patients or because of the supraphysiological doses of GCs used (*Mooij et al., 2010*).

Steroids contribute to elevated cardiovascular diseases partly by changing the levels of lipoproteins that carry cholesterol in blood by increasing levels of LDL and decreasing levels of HDL which may lead to heart attack or

---