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

Thesis

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By

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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

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List of Abbreviations

Δ4A	: 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	: Adrenocorticotropic 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

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	: Intramascular
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

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+	: 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

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-α : Tumor necrosis factor alpha

UGS : Urogenital sinus

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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