بسم الله الرحمن الرحيم

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بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

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Clinical and Biochemical Profile of Patients with 46, XY Disorders of Sex Development

Thesis

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By

Nagwa Mosaed Hassan Ali
M.B.B.Ch. Sohag University

Supervised by

Prof. Dr. Heba Hassan Elsedfy
Professor of Pediatrics
Faculty of Medicine, Ain Shams University

Dr. Salah Mahmoud Mohamed Ebrahim
Assistant Professor of Pediatrics
Faculty of Medicine, MUST University

Dr. Rana Abdelhakim Ahmed Mahmoud
Lecturer of Pediatrics
Faculty of Medicine, Ain Shams University

Faculty of Medicine
Ain Shams University
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To my son and my daughter for their continuous support and love.

Nagwa Mosaed Hassan Ali

Dedication

To:

My parents

for their endless love, support,

and continuous care

&

My Family

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List of Abbreviations

Abb.	Full term
17-OHP	*17-hydroxyprogesterone*
21OHD	*21-hydroxylase deficiency*
5αRD	*5-alpha- reductase*
ACTH	*Adreno corticotrophin hormone*
AIS	*Androgen insensitivity syndrome*
AMH	*Anti-müllerian hormone*
AR	*Androgen receptor*
CAH	*Congenital adrenal hyperplasia*
CAIS	*Complete androgen insensitivity syndrome*
CGH	*Comparative genomic hybridization*
DEA	*Dehydroepiandrosterone*
DHEAS	*Dehydroepiandrosterone sulphate*
DHT	*Dihydrotestosterone*
DSD	*Disorders of sex development*
FISH	*Fluorescent in situ hybridization*
FSH	*Follicle-stimulating hormone*
GH	*Growth hormone*
hCG	*Human chorionic gonadotrophin*
hCG	*Human chorionic gonadotropin*
HS	*Highly significant*
IBM SPSS	*Statistical Package for Social Science*

IGFs	*Insulin-like growth factor system*
LH	*Luteinizing hormone*
NS	*Non significant*
PAIS	*Partial androgen insensitivity syndrome*
S	*Significant*
SRD5A2	*Steroid 5alpha-reeductase type 2*
SRY	*Sex-determining region Y*
T	*Testosterone*
TDF	*Testes-determining factor*

INTRODUCTION

Disorders of sex development (DSD) comprise a wide range of conditions with varying features and pathophysiology that most often present in the newborn or the adolescent. Affected newborns are born with ambiguous genitalia, whereas adolescents present with atypical sexual development during the pubertal years. These clinical situations can often be difficult to manage, particularly in those cases where the sex of rearing is uncertain. Developing a logical and pragmatic plan for investigations while establishing a dialogue and building rapport with the affected child and the parents is crucial to the initial approach and ongoing management ***(García-Acero et al., 2020).***

At birth, patients with 46, XY DSD show diversity of external genitalia patterns ranging from female external genitalia, to ambiguous, and even under virilized male external genitalia ***(Acién and Acién, 2020).*** This is determined by the capacity of the testicles to produce testosterone and transform it into dihydrotestosterone (DHT) by 5-alpha- reductase (5αRD) enzyme as well as the presence of receptors sensitive to testosterone ***(Grinspon and Rey, 2016).***

Mutations in steroid 5αRD 2(SRD5A2) gene impairs the activity of enzyme 5αRD and hence the conversion of testosterone to its more potent form DHT. Individuals with 5αRD are often raised as females due to under masculinized

genitalia but the gender role changes soon after attaining puberty. Mutations in androgen receptor gene may lead to the androgen insensitivity syndrome (AIS) which can be partial androgen insensitivity syndrome (PAIS) or complete androgen insensitivity syndrome (CAIS) and is the most common cause of 46, XY DSD. The spectrum of phenotypes associated with AIS may range from completely female through mixed male/female to completely male type. In 1995, Charmian proposed new grading system for the phenotypic features in AIS based on Prader classification for CAH ***(Vasundhera et al., 2016).***

Individuals diagnosed with 46, XY DSD show an overlap in clinical and biochemical parameters which emphasizes the need for comprehensive evaluation with a multidisciplinary approach.

Aim of the Work

To study the clinical and biochemical profile of a group of patients with 46, XY DSD.

Chapter 1

EMBRYOLOGY AND ENDOCRINOLOGY OF HUMAN GENITAL DEVELOPMENT

Before sexual differentiation begins at 7-8 weeks of gestation the urogenital ridge develops on the posterior abdominal wall from the intermediate mesoderm. The wolffian (mesonephric) and Mullerian (paramesonephric) ducts form and migrate caudally to the cloaca, while the germ cells migrate from the yolk sac into the bi-potential gonad as the mesonephros regresses. At sexual differentiation, Anti-Mullerian Hormone (AMH) and testosterone are secreted from the testis to control ductal development, external genital virilization and descent of the testis into the scrotum ***(Hutson and Bouty, 2020).***

Testes:

If an embryo is a genetic male (46 XY), the bipotential gonad differentiates to testes under the influence of the sex-determining region Y (SRY) gene. SRY is a single exon gene, and it encodes a transcription factor called the testes-determining factor (TDF); this induces male sex determination. SRY gene expression aids in the differentiation of Sertoli cells, which later results in the production of Mullerian inhibiting substance. SRY-type high mobility group box 9 (SOX9) also

helps in the Sertoli cell differentiation, which is up regulated by the SRY gene. It is the critical step in the initiation of testis development ***(Krishan, 2022).***

Initially, gonadal cells segregate into two compartments by invading the gonadal medulla by primitive sex cords and forms testicular cords and interstitial tissue. Testicular cords are composed of germ cells and sustentacular cells of Sertoli. Interstitial Leydig cells lie between the testes cords, which derive from the original mesenchyme of gonadal ridge. Gonadal ridge vascularization is a dynamic process. The XY gonad recruits and patterns vasculature by a remodeling mechanism, whereas developing ovary recruits vasculature by normal angiogenesis. In differentiating testes, pre-existing mesonephric vessels dissociate and form a cluster of endothelial cells that migrate and reach below the coelomic epithelium of gonad, where they assemble to form the coelomic vessel, a vessel that runs the length of the testes at its antimesonephric margin. The formation of this vessel is one of the earliest hallmarks of testes development that distinguishes it morphologically from the developing ovary. Mesonephric ducts form the main genital duct of the male embryo. The remaining parts of the excretory tubules form the efferent ductules these link rete testis and mesonephric duct, which becomes the ductus deferens. The seminiferous tubules and rete testis tubules enter into the ductules efferents ***(Rey et al., 2020).***