Ovotesticular Disorder of Sex Development (OT- DSD) among Egyptian DSD patients

Mona Mekkawy, Alaa K Kamel, Amal M Mohamed and *Inas Mazen
National research Centre. Human cytogenetics dept., *Clinical genetics dept.

Introduction

Ovotesticular disorder of sex development (OT-DSD) is a rare disorder of sexual differentiation characterized by the presence of both testicular and ovarian tissues in the gonads of the same individual. The incidence of OT-DSD ranges from 3% to 10% of all DSD. Patients usually prese,nt at birth with ambiguous genitalia, and the majority show a 46,XX karyotype, with absence of the SRY sequence (Matsui et al., 2011; Khadilkar et al., 2015)

The etiology may be due to 46,XX/46,XY chimerism as a result of fertilization of the ovum and the polar body or tetragametic fusion, mosaicism with various combinations (46,XX/47,XXY, 45X/46,XY) (Paula et al., 2015) or mutations of autosomal or sex chromosome genes involved in the testis-determining pathway.

Objectives

Clinical, histopathological and and Cytogenetic studying of this rare form of Disorders of sex development (DSD) among Egyptian patients.

Patients:

Among 540 DSD patients studied over a period of 5 years (2010-2015) who were referred to the Clinical Genetics and endocrinology Clinic, NRC, Cairo, Egypt, we report 8 patients with OT-DSD, The patients constituted 6% of the patients presenting with ambiguous genitalia and 1.5 % of all patients.

Seven patients presented with ambiguous genitalia, One male patient presented with pubertal breast development.

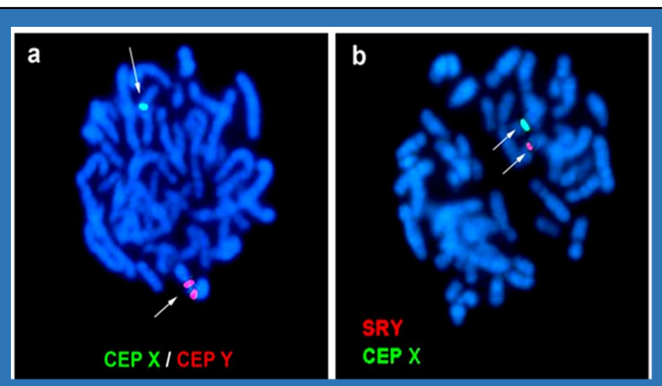
OT-DSD pathological diagnosis was confirmed in all patients.

Methods:

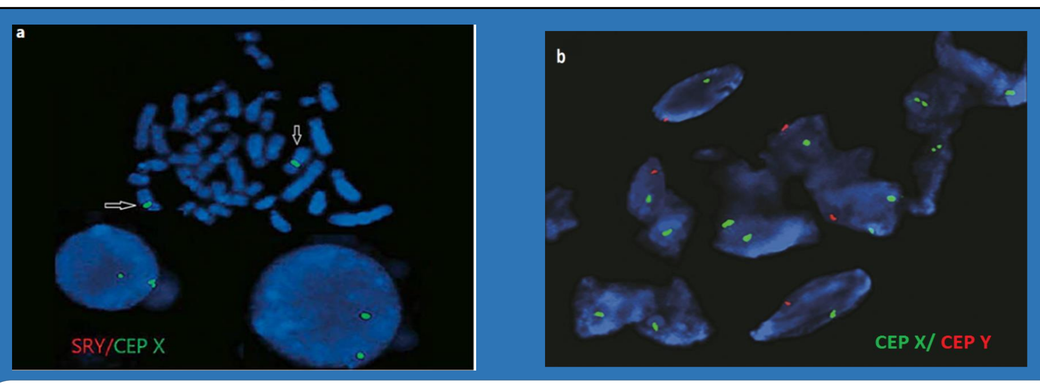
- Detailed clinical examination
- Anthropometric measurements ,Hormonal assay
- Imaging examinations
- Chromosomal analysis and Fluorescence in situ hybridization (FISH)
- Laparoscopy, laparotomy and gonadal biopsy with gonadal histopathological examination. ,FISH on gonadal tissue cells

Results

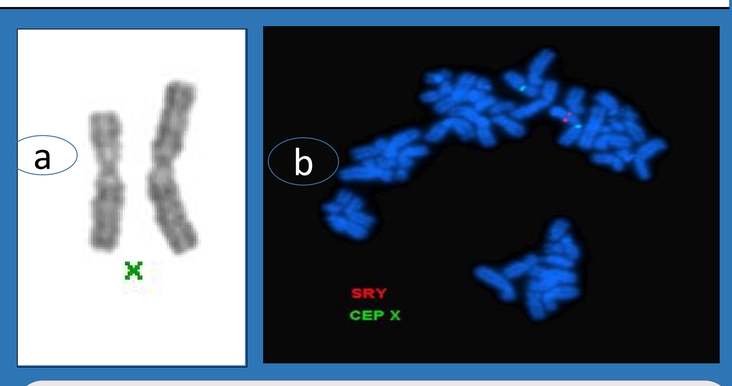
Patient	1	2	3	4	5	6	7	8
Sex of rearing	Female	Female	Male	Female	Female changed to a male	Male	Male	Male
Age (year:month)	13:00	00:09	11:08	3 years	12:00	25:10	00:06	03:06
Laparoscopy	Testis like gonad (inguinal region)/ovary, Hypoplasic uterus	Dysgenetic testis (inguinal region)/ovary, Left fallopian tube, uterus.	A uterus and a left gonad, right scrotal swelling.	Prepubertal uterus and bilateral gonads.	Prepubertal uterus and no gonadal tissue visualized.	Right side Fallopian tube and a small cystic ovary, uterus, left side gonad appeared as testes	Normal size left testis with minimal hydrocele, Right gonad not detected.	A uterus and two gonads
Pathology	Right: dysgenetic testis, Left: ovary with some follicular activity	Right: Dysgenetic testis, left: ovotestis	Both testicular and ovarian tissues within the left gonad. Rt scrotal epididymal cyst.	Bilateral ovotestis. testicular	Left dysgenetic testis, right ovotestis	testicular biopsy: testicular tissue showing small tubules, lined by sertoli cells.	left testicular tissue, right ovotestis	Both testicular and ovarian tissues in the left gonad., Rt. Testicular tissues
Cytogenetic results	45,X [60]/46,X, idic(Y)(p11.32)[40]. ish idic(Y)(p11.32) (wcpY+, Xp/Yp-, SRY+, DYZ3++)	45,X[75]/46,X, idic(Y)(p11.32)[15]/ 47,X,idic(Y)(p11.32)x2[4]/ 46,XY[6] ish idic(Y)(p11.32) (wcpY+, Xp/Yp-, SRY+, DYZ3++)	mos 46,X,dic(X;Y)(p22.33;p11.32)[65]/45,X[23]/45,dic(X;Y)(p22.33;p11.32)[12]. ish: t(X;Y)(p22.33;p11.32)(DXZ1+/DYZ3+, KAL+, SHOX–, Xp–/Yp–, SRY+).	46,XX ish: (DXZ1++/DYZ3-, SRY-)	46,XX ish: (DXZ1++/DYZ3-, SRY-)	46,XX ish: (DXZ1++/ SRY-)	46,XY[70]/ 46,XX[30]	46,XX ish: (DXZ1++/DYZ3-, SRY-)
FISH on gonadal tissue			nuc ish X/Ycen(DXZ1x2,DYZ3x1)(DXZ1 con DYZ3x1) [67]/ (DXZ1x1)[23]/(DXZ1x1,DYZ3x1)(DXZ1 con DYZ3) [10]	nuc ish X/Ycen (DXZ1x1)[35]/ (DXZ1x2) [55]/ (DXZ1x1,DYZ3x1) [10]	nuc ish Xcen(DXZ1x2), Yp11.32 (SRY-)			



a) FISH analysis showing two hybridization signals for the Y centromere probe (DYZ3); (b) one signal for LSI SRY probe



a) FISH analysis on blood metaphase and interphase cells of patients 4 showing two hybridization signals for X centromeres (DXZ1).
b) FISH on gonadal tissue cells showing three cell lines revealing: two hybridization signals for the X centromere, one X centromeric signal and hybridization signals for both CEP X and CEP Y.



a) GTG partial karyotype for the normal and derivative X chromosomes.
b) FISH showing a hybridization signal for the SRY gene probe on the translocation chromosome

Conclusions:

- OT DSD should be considered as one of the **differential diagnoses in cases of ambiguous genitalia** with non palpable or asymmetrical gonads, pubertal gynecomastia, and cyclical hematuria, irrespective of the karyotype or internal genitalia.
- **Gonadal biopsy** is important in to establish diagnosing cases of sex chromosome mosaicism.
- **Chromosome studies** carried out on peripheral lymphocytes do not always reflect the proportion of cell lines in the gonads.

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Mona Mekkawy
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