ENVIRONMENTAL AND GENETIC EVALUATION IN 46,XY DISORDERS OF SEX DEVELOPMENT

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ABSTRACT

The phenotype of Disorders of Sex Development (DSD) patients depends on many factors including the presence of Copy Number Variation (CNVs) of different genes. The unbalanced rearrangement and the presence of deletions or duplications affect dramatically the phenotypic sex. The aim of this study is to correlate genotypic abnormalities with clinical phenotype in 46,XY DSD patients by Multiplex Ligation dependant Probe Amplification (MLPA**)** technique for accurate diagnosis in these patients and study possible paternal and maternal exposure to environmental risk factors in these cases. This study reported on forty patients with variable presentations of disorders of sex development (DSD) presenting with ambiguous genitalia, hypospadias, micropenis or with female phenotype with primary amenorrhea or short stature, with exclusion of cases with disorders in androgen synthesis. A complete personal, family history and clinical examination were done. Parents were asked to fill a questionnaire about frequency of dealing with some environmental factors including smoking, caffeine and using some materials having estrogenic effect as plastics, insecticides, and others. Conventional cytogenetics studies and fluorescence in situ hybridization (FISH) on peripheral blood as well as DNA extraction and Multiplex Ligation-dependent Probe Amplification **(**MLPA) were done for all cases for some genes; DMRT1, CYP17A1, SRD5A2, HSD17B3, DAX1, CXor21, SOX9, SRY, ZFY, WNT4 and SF. Results showed 46,XY was shown in all patients. MLPA analysis showed Copy Number Variation (CNVs) in 15% of cases. The study showed duplication of DMRT1 in 5% patients, deletion of SRY 2.5% patients, deletion of SOX9 in 5% patients, duplication of DAX1 in 12.5% patient, duplication of CYP17A41 in 5% patients, deletion of

DMRT1 in 12.5% patient, duplication of SRD5A in 2.5% patient and duplication of HSD17B3 in 2.5% patient. Maternal exposure during pregnancy and paternal exposure to Endocrine Disrupting Compounds (EDCs) were insignificantly associated with DSD compared to control cases. This study demonstrates the importance of proper detection of genetic mutation in DSD patients showing a discrepancy between their karyotype and gonadal phenotype. It was concluded that using MLPA is recommended for better understanding of the phenotype with other recent techniques as for better diagnosis and follow up.
Key Words: Disorders of sex Development, Multiplex Ligation Probe Amplifications, Copy Number Variations, Endocrine Disrupting Compounds.

INTRODUCTION

Sex of rearing depends on many factors; genetic sex, degree of virilization of external genitalia, prospects of restoring normal appearance of external genitalia, fertility. Genital surgery is often required; but still the type and time of surgery are debatable (Walia *et al.,* 2018*).*

Disorders of sex development (DSD) are a group of heterogeneous conditions with diverse pathophysiology. They are generally characterized by an abnormality of the chromosomal, gonadal or phenotypic features that typically define sex development. Such conditions usually present with atypical genitalia in the newborn period or as delayed puberty in an adolescent or present later in life as infertility *(*Hughes *et al.,* 2008*).*

A number of genes are contributed to both early and late sex determination and differentiation. *NR5A1, WT1, DAX1, SOX9, SRY and DMRT1* are genes required for the formation of the bipotential gonadal ridge *(*Wilhelm *et al.;* 2007*).* *DMRT1* is suggested to have an important role in sex differentiation. Some DSD cases are due to haploinsufficiency of *DMRT1* gene located on chromosome 9 (Marsudi *et al.,* 2018*).* Also 5-alpha-reductase is involved in

male sexual development by converting testosterone to DHT in males. Previous studies reported that SRD5A2 gene mutations is behind 46,XY DSDs in some cases (Fu *et al.,* 2016*).*

Classification of disorders of sexual development (DSD) was modified to include three broad groups: sex chromosome DSD, 46,XX DSD, and 46,XY DSD.46,XY DSD has three broad categories; Disorders of gonadal development, Disorders in androgen synthesis or action and other causes as hypogonadotropic hypogonadism, cryptorchidism, and isolated hypospadius *(*Hughes *et al.;* 2006*).* 46,XY DSD is the commonest of DSD cases (65.9%) (Mazen & Ismail, 2010*).*

Several environmental pollutants, including organoclorine pesticides, polychlorinated biphenyls, bisphenol A, phthalates, dioxins and furans have estrogenic and anti androgenic activity and are thus considered as EDCs. Male sex differentiation is critically dependant on the normal production and action of androgen during fetal life. So EDCs may alter normal sex differentiation *(*Gaspari *et al.;* 2011*).* A study suggested that paternal environmental exposures may increase the risk of genital abnormality in newborn boys, which may indicate an effect on the paternal germline. Genital ambiguity was associated with paternal exposure to pesticides, and was found more frequent in fathers who were active smokers *(*Pierik *et al.,* 2004*).* Fetal exposure to endocrine disruptors with estrogen-like or antiandrogen-like activity through their mothers has been suggested as a cause for testicular dysgenesis *(*Sharpe, 2012*).*

Genetic testing is recognized as a key element in the investigation of individuals with a suspected DSD. The first line investigation of a possible DSD includes karyotype and FISH analysis, which is crucial when there is uncertainty

about sex assignment but also is an important guide for management *(*Schober *et al.;* 2012*).*

This study aimed at clarifying the possible paternal and maternal environmental risk factors leading to 46,XY DSD and correlating genetic abnormalities detected with the clinical features of 46,XY DSD.

SUBJECTS AND METHODS

The study was carried out on selected forty cases of 46,XY DSD patients from cases referred from the Endocrinology Clinical Genetics Department, Centre of Excellence, National Research Centre (NRC) to the Human Cytogenetics Department. Selected cases included patients presenting with ambiguous genitalia, hypospadias, infertility, and micropenis or female phenotype with short stature or primary amenorrhea with exclusion of cases with disorders in androgen synthesis. Age ranges from birth to adulthood. Patient's mothers were subjected to a questionnaire, previously was used in a European community study, but modified; for residence, occupation, supplements, drugs, exposure to some products with EDCs. Fathers will be subjected to questionnaire on lifestyle, occupation and exposures to EDCs commonly used in daily living according to USEPA (United States Environmental Protection Agency) (Gaspari *et al.*, 2011*).*

Parents of forty normal individuals with age matching the patients were included in the study as control group. Control group was approached consecutively and an informed consent was obtained from patients/control group or legal guardians.

Patients were subjected to clinical evaluation for disorders of sex development, which is done by the clinical team was included; Full history and pedigree analysis. Thorough clinical examination with special emphasis on the phenotypic description of external genitalia was classified according to Quigley et al., (1995). Pelvic ultrasonography was done for evaluation of internal genitalia. Hormonal studies in the form of serum Testosterone, delta 4 androstenedione DHT, both basal and after HCG stimulation as well as basal serum FSH and LH. Psychological Assessment of masculinity | feminity index was also done. Histopathology evaluation was when indicated for proper diagnosis. Conventional cytogenetics analysis was carried out on peripheral blood lymphocytes, using GTG banding technique according to Verma and Babu. (1995). DNA was extracted from 5ml venous blood and Multiplex Ligation-dependent Probe Amplification (MLPA) was done for all patients also FISH technique was done for some cases. Data analysis was done using the statistical package for social sciences (SPSS) version 23. Chi square tests were used for evaluation of data; statistical significance was set at 0.5.

Challenges faced during conducting the research were in the selection of the samples to be included in the study. Forty cases were selected from hundreds of patients suffering from 46,XY DSD attending the Endocrinology Clinical Genetics Department, Centre of Excellence, National Research Centre (NRC).

RESULTS

The study included 40 patients. Positive parental consanguinity was present in 57.5%. According to sex of rearing, 70% were reared as males and 30% were reared as females. Patients presented with ambiguous genitalia were 52.5%,

20% with hypospadias, 17.5% with primary amenorrhea, 5% with infertility, 2.5% with inguinal hernia and 2.5% with short stature. Cytogenetic analysis using conventional GTG banding technique was done on peripheral blood lymphocytes for all patients. 46, XY was shown in all patients. MLPA analysis was conducted on 40 patients. The results of the current study showed 15% with clinical CNVs. Duplication of DMRT1 was detected in 5% patients, deletion in SRY was detected in 2.5% patients, and deletion in SOX9 was detected in 5% patients, duplication in CYP17A41 in 5% patients, deletion in DMRT1 in 2.5% patient, duplication in SRD5A in 2.5% patient and duplication in HSD17B3 in 2.5% patient. Data are summarized in table (1).

Table (1): Summary of reported findings in the study:

Case	age	Sex of rearing	presentation	External genitalia	karyotype	MLPA
1	1 month	Male	Ambiguous genitalia	Ambiguos genitalia Q:3	46,XY	dupDMRT1, dup CYP17A1, dup SRD5A2
2	4 years	Male	ambiguous genitalia	left undescended testis Q: 2	46,XY	del SOX9
3	3 years	Male	ambiguous genitalia	bilateral undescended testis Q:4	46,XY	del SOX9
4	16 years	female	short stature	normal female external genitalaia.Q:6	46,XY	del Sry
5	1 year	Male	ambiguous genitalia	bilateral undescended testis Q: 4	46,XY	del DMRT
6	15 years	Male	ambiguous genitalia	Bilateral undescended testis, hypospadius Q:3	46,XY	dupDMRT1, dup CYP17A41, dup HSD17B3

*Q: Quigley score.

Table (2): Frequent distribution of results of MLPA in the study

MLPA results	Number	Percentage
del SRY	1	2.5%
del DMRT	1	2.5%
dupDMRT1	2	5%
dup CYP17A41	2	5%
dup HSD17B3	1	2.5%
del SOX9	2	5%
dup SRD5A2	1	2.5%

Table (3): Characteristic features of the studied patients

Features		Cases	
		Count	%
Sex	Male	29	70%
	Female	11	30%
Consanguinity	Positive	23	57.5%
	Negative	17	42.5%
presentation	Ambiguous genitalia	21	52.5%
	Hypospadias	8	20%
	Primary amenorrhea	7	17.5%
	infertility	2	5%
	Short stature	1	2.5%
	Inguinal hernia	1	2.5%
Copy number variation	Detected	6	15%
	not detected	34	85%

This study has evaluated the frequency of exposure to certain environmental materials; pesticides, soda cans, canned food, plastic cups and smoking, to the parents of patients compared to parents of normal patients (control group). There was no significant association with exposure to some environmental materials to the parents of DSD patients. The data is summarized in table (2) and (3) for comparison Chi square was used.

Table (4): Frequency of dealing of fathers with some sources of EDCs:

Fathers		Cases		Controls		p value
		No	%	No	%	
Smoking	Daily	23	59.0	22	56.4	0.971
	Never	3	7.7	3	7.7	
	Occasionally	13	33.3	14	35.9	
Plastic Cups	Daily	27	69.2	28	71.8	0.804
	Occasionally	12	30.8	11	28.2	
Plastic Bottles	Daily	32	82.1	32	82.1	1.000
	Occasionally	7	17.9	7	17.9	
Plastic Bag	Daily	32	82.1	33	84.6	0.761
	Occasionally	7	17.9	6	15.4	
Vegetarian Food	Daily	17	43.6	15	38.5	0.645
	Occasionally	22	56.4	24	61.5	
Insecticide	Daily	9	23.1	9	23.1	1.000
	Occasionally	30	76.9	30	76.9	
Soda Can	Daily	23	59.0	24	61.5	0.817
	Occasionally	16	41.0	15	38.5	
Food Can	Daily	8	20.5	8	20.5	0.923
	Never	3	7.7	4	10.3	
	Occasionally	28	71.8	27	69.2	
Detergent and cleaning agents	Daily	8	20.5	7	17.9	0.955
	Never	12	30.8	12	30.8	
	Occasionally	19	48.7	20	51.3	

P≤0.05 is considered statistically significant, analysis done by chi square test.

Table (5): Frequency of dealing of mothers with some sources of EDCs:

Mothers		Cases		Controls		p value
		No	%	No	%	
Smoking During Pregnancy	Daily	1	2.6	1	2.6	1.000[a]
	Never	34	87.2	35	89.7	
	Occasionally	4	10.3	3	7.7	
Plastic Cups	Daily	25	64.1	25	64.1	1.000
	Occasionally	14	35.9	14	35.9	
Plastic Bottles	Daily	35	89.7	34	87.2	1.000[a]
	Occasionally	4	10.3	5	12.8	
Plastic Bag	Daily	25	64.1	24	61.5	0.815
	Occasionally	14	35.9	15	38.5	
Vegetarian Food	Daily	17	43.6	16	41.0	0.819
	Occasionally	22	56.4	23	59.0	
Insecticide	Daily	9	23.1	9	23.1	1.000
	Occasionally	30	76.9	30	76.9	
Drugs & Supplements	Daily	20	51.3	22	56.4	0.892
	Never	3	7.7	3	7.7	
	Occasionally	16	41.0	14	35.9	
Soda Can	Daily	16	41.0	16	41.0	0.894
	Never	3	7.7	2	5.1	
	Occasionally	20	51.3	21	53.8	
Food Can	Daily	9	23.1	11	28.2	0.741
	Never	6	15.4	4	10.3	
	Occasionally	24	61.5	24	61.5	
Detergent and cleaning agents	Daily	26	66.7	26	66.7	1.000
	Occasionally	13	33.3	13	33.3	
Cosmetics of unknown source	Daily	15	38.5	15	38.5	1.000
	Never	5	12.8	5	12.8	
	Occasionally	19	48.7	19	48.7	

$P \leq 0.05$ is considered statistically significant, analysis done by chi square test, a: analysis done by fisher exact test

DISCUSSION

Development of male reproductive system is a complex process controlled by sophisticated networks that depends on sex-specific differentiation and endocrine function. These regulatory cascades are often illustrated by high prevalence of genitourinary defects in newly born. These urogenital anomalies are usually difficult challenges for both parents and physicians.

Dessouky *et al.,* 2001 stated that childhood is the most common group of presentation; this is similar to our study as we reported the ages at presentation ranged between few days and 20 years with a mean of 5.5 years.

In agreement with our study that showed the main complaints at presentation were ambiguous genitalia in 25%, short stature in 20%, hypospadias in 10%, primary amenorrhea in 10%, 5% in infertility and short stature in 30%, also Sema *et al.,* 2011 mentioned nearly same percentages.

This study showed 57.5% had positive consanguinity also Shawky *et al.,* 2011 reported that consanguineous marriage was reported among 55.56% of patients and also Mazen & Ismail 2010 mentioned that high degree of consanguinity in DSD was also reported in Egypt 61–65%.

Kafla *et al.,* 2015 stated that EDCs can cause genital abnormalities as hypospadias. Since EDCs are present in variable mixtures, so their effects are time-dependent and sometimes hard to detect. Specific causes of most of genital and urinary tract defects are still unknown. Allali *et al*., 2011 mentioned that quantification of exposure to these EDCs is particularly difficult and the use of questionnaires may not be reliable enough which is in agreement with our results.

The results of the current study showed 15% with clinical CNVs using MLPA, it is considered a reliable tool for diagnosis , this is in agreement with Harisson *et al*., 2013 who performed MLPA to screen for deletions or duplications for *SOX9, NR5A1 (Sf-1), WNT4 and DAX1*. Kim *et al*., 2015 also reported that molecular cytogenetic analyses using MLPA would be beneficial for patients with 46,XY DSD, because identification of pathogenic CNVs could help to predict the disease outcome and possible complications of patients. Furthermore, detection of disease-associated CNVs significantly improves the accuracy of genetic counseling for patients' families.

Deletion of *SRY* in 2.5% of patients in the study was less than results reported by Philibert *et al.,* 2007 who emphasized on the importance of investigating the *SRY* gene as a first step for 46,XY DSD patients; however, only 10%-20% of 46,XY gonadal dysgenesis patients show *SRY* gene CNVs.

In this study *DMRT1* deletion was found in a phenotypically male patient presenting with ambiguous genitalia unlike Eser and Ayaz 2018 who studied a case of phenotypically female with 46,XY who showed by further genetic analysis deletion of *DMRT1* genes. They stated that few cases of XY DSD caused by *DMRT1* gene abnormality reported. In addition, the pathomechanism has not been fully understood that would explain *DMRT1* duplication in our patients that require further study.

The current study reports that *CYP17A1* gene duplication in 5%, also Simiao *et al.,* 2016 concluded that 17α-hydroxylase is a rare, unusual and challenging to diagnose endocrine disorder and was the first to demonstrate that mutations in the *CYP17A1* gene may be used for the diagnosis in the

17α-hydroxylase patient without typical clinical symptoms. Diagnosis of 17α-hydroxylase is confirmed by *CYP17A* mutation analysis.

Kim *et al* 2015 stated that deletions involving this region of *SOX9* can result in a wide spectrum of sex development in 46,XY DSD, ranging from nearly normal male phenotype to nearly complete female phenotype and that comes in agreement with our findings in 5% with del *SOX9.*

Disorders of gonadal differentiation is accompanied with mutation of *SRD5A2* in 2.5% of our patients who showed duplication of *SRD5A2* is explained by Byers *et al* 2017 who reported that the severity appears to correlate with the genotype of *SRD5A2* in 46, XY DSD patients.

CONCLUSION AND RECOMMENDATION

Molecular cytogenetic analysis should be included in the diagnostic workup of patients with 46,XY DSD. MLPA appear to be useful for molecular diagnosis of patients with 46,XY DSD. It is also suggested that exposure of environmental risk factor to both mother and father was found to be not associated with genital development. Environmental risk factors are difficult to assess and may require other methods with the use of questionnaires.

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التقييم البيئى والوراثى لمرضى خلل التكوين الجنسى (كروموسوم اكس واى ٤٦)

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المستخلص

تنتج مشكلة خلل التكوين الجنسى عن عدة عوامل باثوفسيولوجية حيث أنها من الممكن أن تظهر بصور اكلينيكية مختلفة فى الاطفال حديثى الولادة أو فى فترة المراهقة أو حتى فى صورة تأخر الانجاب. وتساهم مجموعة من الجينات فى التطور الجنسى الطبيعى, الموجودة على الكروموسومات والتى يعتبر وجودها ضرورى لاتمام عملية التكوين الجنسى السليم، كما يعتبر وجود جينات معين فى الجنين الحامل للكروموسومات اكس، واي يساعد على التطور الطبيعى للخصية وذلك تحت تأثير الهرمونات الذكورية ومنع ظهور تأثير الجينات الانثوية الذين يؤدوا إلى تطور الغدد الجنسية الى مبايض، ويتم تقسيم خلل التكوين الجنسى الى ثلاث مجموعات كبيرة ويتضمنها عدة مسميات أخرى والتى تظهر اكلينيكيا بصور مختلفة. وقد لوحظ من خلال الأبحاث أن التعرض إلى بعض المؤثرات البيئية وهى المركبات الى تتداخل مع الهرمونات قد تؤدى الى خلل التكوين الجنسى وخلل فى الغدد الجنسية. وقد أثبتت دراسات أخرى أن تعرض الآباء الى المؤثرات البيئية مثل بعض الكيماويات أو المبيدات أو التدخين قد يؤدى إلى ظهور خلل التكوين الجنسى أو ظهور الاعضاء الجنسية الخارجية المبهمة.

خطة البحث: الدراسة تمت لعدد ٤٠ حالة من مرضى خلل التكوين الجنسى ٤٦، اكس واى والذين يعانون من صفات مرضى خلل التكوين الجنسى وتم اختيارهم من عيادة الوراثة الاكلينيكية بالمركز القومى للبحوث. تم أخذ التاريخ الطبى والمرضى الكامل للحالة والتاريخ المرضى للعائلة كما تضمن ايضا استبيان للام فى فترة الحمل وما تعرضت له الأم من أدوية أو التعرض للمبيدات أو لبعض الكيماويات.كما ايضا اخذ استبيان للاب عن طبيعة العمل وإذا كان يتعرض لبعض المؤثرات البيئية فى صورة كيماويات أو التدخين أو مبيدات. والفحص الاكلينيكى الشامل للمريض والتقييم للشكل الظاهرى للحالات وفحص الموجات الصوتية. كما تم عمل قياس للهرمونات ودراسة الكروموسومات بطريقة التحزيم التقليدى واستخدام مجسات التهجين الفلورسنتى للكشف عن وجود خلل فى بعض الحالات كذلك استخلاص الحمض النووى وقياس تركيزه كما تم استخدام تقنية الملبا للكشف عن وجود خلل بالجينات.

نتايج البحث: تم الكشف عن وجود اختلال جينى فى ١٥% من الحالات كما انه كانه لا يوجد ترابط بين تعرض آباء وأمهات الحالات لبعض المؤثرات البيئية التى قد تسبب ظهور خلل فى التكوين الجنسى.

الاستنتاج والتوصيات: من المهم استخدام التقنيا الجزيئية الوراثية الحديثة مثل تقنية الملبا بالمعامل للكشف عن وجود خلل جينى فى مرضى خلل التكوين الجنسى وذلك للوصول للتشخيص السليم وللمتابعة

وأيضا الفحص العائلى لبعض الحالات. كما يفضل استخدام وسائل أخرى مع الاستبيان للوصول للمخاطر البيئية التى قد يتعرض لها الأب والأم لمثل هذه الحالات.

الكلمات الدالة: خلل التكوين الجنسى، تقنية الملبا،طفرات عددية بالجينات،المركبات المعطلة للهرمونات.