University Pediatric Clinic, Skopje, N.Macedonia
Department of Endocrinology and Genetics

Difficulties in diagnosing variable disorders of sexual development

Sukarova-Angelovska Elena, Krstevska-Konstantinova Marina, Alulovska Natasa, Ilieva Gordana, Anastasovska Violeta

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Introduction:

Disorders of sexual development (DSD) include etiologically heterogeneous group of patients that have disorders of genital development. Consensus guidelines that are currently used, divide all DSD in three main groups - sex chromosomal abnormalities, XX or XY DSD, all divided in subgroups in dependence of genetics and hormonal tests. The phenotypic spectrum of external genitalia, gonads and development of Wolfian and Mulerian duct derivatives varies in all patients. Many syndromic cases stayed unclassified and without easily reached etiology.

Materials and methods

14 patients with syndromic DSD were evaluated. All patients have ambiguous genitalia with different Prader staging. Phenotypic recognition, imaging, as well as karyotypic, hormonal and biochemical tests were evaluated in all. Excluded from the group: CAH, Turner sy, Klinefelter sy, isolated hypospadia, Swyer, AIS, Meyer-Rokitanski.

- 11 with XY karyotype, (3 SRY positive)

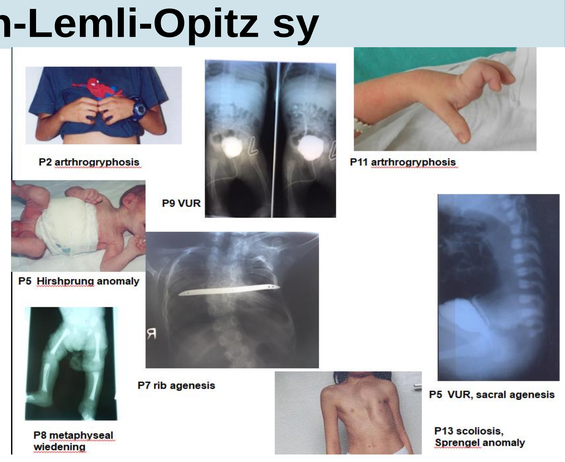
	karyotype	SRY	Barr bodies	Prader staging	
P1	46,XY	/	-	P2	Costello syndrome
P2	46,XY	/	-	P4	Distal artrogryphosis
P3	46,XY	/	/	P4	Multiple synphalangism sy
P4	46,XY	-	/	P3	Vater sy
P5	46,XY	-	-	P2	Vater sy
P6	46,XY	+	-	P3	Del Y
P7	46,XY	/	-	P3	MURCS
P8	→	+	-	female	46,XY,del 9p
P9	→	+	-	female	46,XY, der(10q), t(Xp;10q)mat
P10	→	/	-	P2	46,XY,der(9p), t(4q;9p)mat
P11	46,XY	+	-	P3	Smith-Lemli-Opitz sy

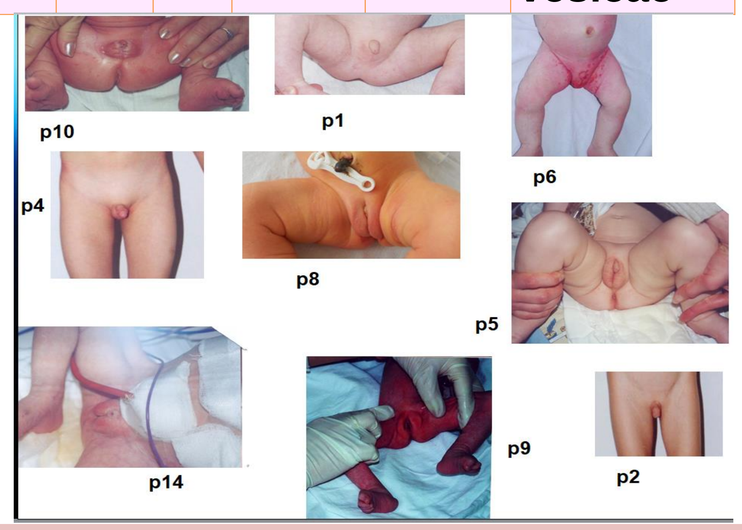
- 3 with XX karyotype, (2 SRY negative)

	karyotype	SRY	Barr bodies	CAH screen	Prader staging	
P12	46,XX	-	+	-	P5 dupl penis	??
P13	46,XX	-	+	-	P1	MURCS
P14	46,XX	/	+	/	P2	Extrophy vesicae

Associated anomalies

System	Patiens	More frequent
CNS	6	Hydrocephalus, corpus callosum agenesis, microcephalus, hypoplasio vermis
Developmental delay / mental retardation	9 (2 early neonatal deaths)	Mild/moderate/severe
Cardiovascular system	5	VSD, ASD, Tetralogia Fallot, atresio a.pulmonalis, hypoplastic right ventricle
Intestinal system	3	Anal atresia, Hirshprung, esophageal fistula
Urinary system	5	Kidney agenesia/hypoplasia, VUR, vesical extrophy
Musculo-skeletal system	10	Artrogryphosis, rib agenesia, vertebral anomalies, sacral agenesia, metaphyseal flaring, pes equinovarus, Sprengel anomaly

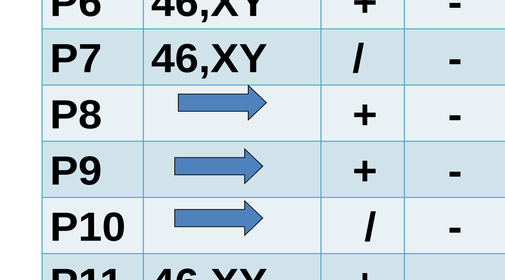




Some mechanisms proven

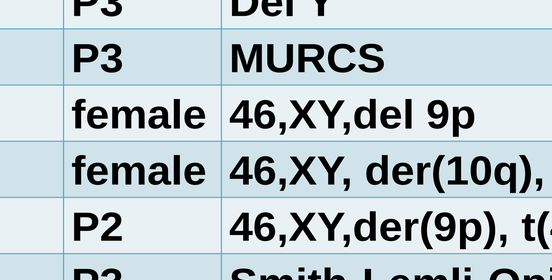
DMRT1/DMRT2 gene haploinsuficiency:

p10



46,XY,der(9p), t(4q;9p)mat

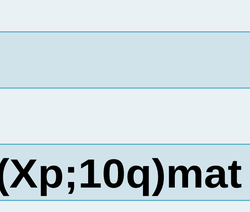
p8



46,XY,del(9p), inv (9p;q)pat

P6

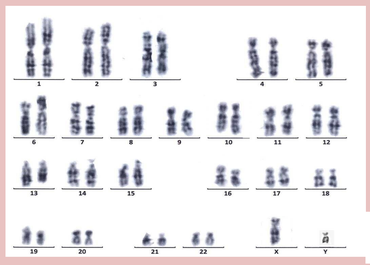
SRY +, profound MR, hypoplasio testis

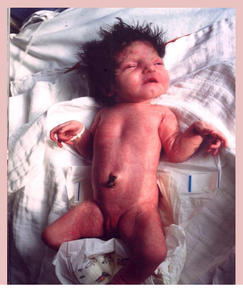


46,XY,del(Yq)

Overexpression of the DAX1 gene located on DDS region:

P9



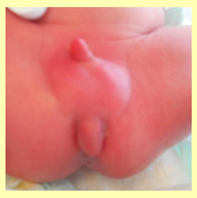


46,XY, t(X;10)mat

Some mechanisms still uknown

P12

46,XX
CAH screen negative
SRY negative
Barr body –positive
Anal atresia
Hirshprung
Sacral agenesia



Discussion and conclusion

The diagnosis of DSD in the neonatal period represents one of the conditions that need urgent diagnosis and in some cases, early treatment. In some cases the condition stayed undetected till puberty. Clinicians often face many difficulties in performing and providing all necessary genetic and laboratory tests. Clinical workout and diagnostic evaluation paths were constructed in order to facilitate gender assignment in infants as soon as possible. Some of the investigations are not easily available, they are time-consuming, also some conditions still don't have proven molecular defect.
Advances in identification of the molecular and hormonal defect, as well as multidisciplinary approach improved the medical care, psycho social and ethical issues in patients with DSD.