BILATERAL TESTICULAR REGRESSION
ETIOLOGY AND OUTCOME IN A LARGE BELGIAN SERIES

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KEY MESSAGES

- Prenatal or obstetric complications in 50%
- 3/33 (9.1%) had (likely) pathogenic *DHX37* variants
  - More severe phenotype indicating early bilateral testicular regression
  - Little penile growth after childhood IM testosterone
- Testosterone replacement therapy resulted in satisfactory pubertal height gain

INTRODUCTION

The etiology of bilateral testicular regression (BTR) remains unexplained in the majority of cases. Evidence supporting both a vascular and genetic origin have been reported. However, whether different etiologies result in different clinical subgroups is unclear. Furthermore, long-term outcome data of individuals with BTR regarding statural and penile growth are very scarce.

AIMS

To assess the underlying factors associated with the development of BTR (*i.e.* pregnancy, neonatal and genetic factors) and explore long-term growth and pubertal outcomes

METHODS

Participants: Individuals born with BTR (n=33) recruited in five Belgian centers at an age of 14.2 ± 5.3 years
Cross-sectional study: Clinical and genital exam
Retrospective data: Initial presentation and management
Genetic analysis: Exome-based testing of genes (n=241) involved in gonadal development and spermatogenesis

RESULTS

Conception, pregnancy and birth

Birth weight (SD)	-0.39 ± 0.93
Birth length (SD)	-0.24 ± 0.82
Gestational age	40.0 (IQR: 2.0)
Preterm birth	4/30 (13.3%)
Use of ART	IVF: 1/31 (3.2%) ICSI: 1/31 (3.2%)
Consanguinity	2/33 (6.1%)
Pregnancy complications	10/22 (45.5%)
Twin pregnancy	4/22 (18.2%) Monozygotic twin: n=3 Triplets (unknown zygosity): n=1
Pre-eclampsia	1/22 (4.5%)
Gestational diabetes	1/22 (4.5%)
Maternal substance abuse	1/22 (4.5%)
Other*	3/22 (13.6%)
Obstetric complications	2/22 (9.1%)

ART: assisted reproductive techniques; MZ: monozygotic twins; *: includes severe maternal anemia with need for transfusions, CMV infection and amniocentesis

Phenotype at first presentation

Age at first presentation:
- Median: 1.2 (2.5) years
- Range: 0 - 14 years

Ambigous genitalia:
- Micropenis/small phallic structure: 8/32 (25.0%)
- Partial fused scrotum (n=1)
- Female gender of rearing (n=1)

Management and puberty

Testosterone treatment during childhood:
- 9/32 (28.1%); Median age: 6.0 (IQR: 10.3)
- IM Sustanon© 25mg/4weeks: 3-6months
- Little to no effect in 2/6 (33.3%)

At study visit:
- Age: 14.2 ± 5.3 years
  - Prepubertal: 15/33 (45.5%); Endpubertal: 14/33 (42.4%)
- Testosterone replacement therapy: 21/32 (65.6%)
  - Median dose: 100mg/2weeks (Range: 16.6-186)

Growth:
- Adult height: 176.5 ± 5.6 cm
  - Target height reached: 14/14 (100%)
- Peak height velocity: 9.4 ± 1.6 cm
- Growth puberty: 24.0 ± 6.7 cm

Stretched penile length:
- 9.6 ± 3.1 cm (< 7cm: n=1)

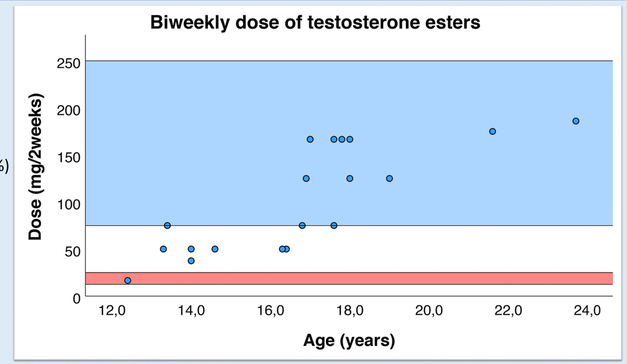

Figure. Scatterplot of biweekly dose of testosterone esters. Lower range (red) represents recommended starting dose; Upper range (blue) represents recommended adult dose.

Genetics

A. (likely) pathogenic variants

	Phenotype	Gene	Transcript	HGVS transcript	HGVS Protein	rsID	REVEL score	GnomAD VAF	GnomAD Homozygotes
Case 1	BTR, micropenis	DHX37	NM_032656.4	c.923G>A	p.(Arg308Gln)	rs1384892917	0.451	0.00001314	0
Case 2	BTR, micropenis, partial scrotal fusion	DHX37*	NM_032656.4	c.923G>A	p.(Arg308Gln)	rs1384892917	0.451	0.00001314	0
Case 3	BTR, micropenis	DHX37	NM_032656.4	c.1000C>T	p.(Arg334Trp)	-	0.595	-	-

B. Variants of unknown significance

	Phenotype	Gene	Transcript	HGVS transcript	HGVS Protein	rsID	REVEL score	GnomAD VAF	GnomAD Homozygotes
Case 4	BTR	SOX8	NM_014587.5	c.200G>A	p.(Cys67Tyr)	-	0.668	-	-
Case 5	BTR	WT1	NM_024426.6	c.1063T>C	p.(Cys355Arg)	rs142059681	0.807	0.0004686	0
Case 6	BTR	PROKR2	NM_144773.3	c.868C>T	p.(Pro290Ser)	rs149992595	0.939	0.00009856	0

All variants are heterozygous. *: segregation analysis revealed maternal inheritance. REVEL score: rare exome variant ensemble learner; VAF: variant allel frequency; Homozygotes: reported number of homozygotes.

Clinical information:
- Case 1 & 3: little to no penile growth after IM testosterone treatment
- Case 2: female gender of rearing

CONCLUSIONS

- Pregnancy and obstetric complications were found in over half of cases
- No new genes were identified
- *DHX37* variants were identified in three cases:
  - All had micropenis/small phallic structure at birth
  - Two cases were treated with (dihydro)testosterone during infancy and showed little to no penile growth
- Pubertal height gain is satisfactory

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