ADOLESCENTS & YOUNG ADULT MEN WITH HYPOSPADIAS:
TESTICULAR FUNCTION AND IN-DEPTH GENETIC SCREENING


KEY MESSAGES
- Hormone levels were reassuring
- Oligo-/azoospermia: 30% of AGA cases with complex hypospadias
- 60% of SGA cases
- No pathogenic monogenic variants or oligogenic variant combinations found

INTRODUCTION
Background: Hypospadias affects approximately 1/200 newborn males and is sometimes included in the D50 spectrum. Few data currently support this hypothesis.
Aims: To assess endocrine and reproductive outcome of young men born with hypospadias and explore genetic mechanisms underlying the development of hypospadias and eventual testicular dysfunction.

METHODOLOGY
Study design: Cross-sectional study (Ghent and Vienna University Hospitals)
Participants: Young adult men (16-21 years) born with non-syndromic hypospadias (n=193) and healthy male controls (n=50)
Assessments: Physical exam, hormonal status (gonadotropins, androgens, insulin-like factor 3 (INSL3) & inhibit B), semen analysis and molecular genetic analysis (NGS-based panel of 474 genes & Oligogenic Resource for Variant Analysis (ORVAL))

RESULTS
Physical exam & hormone assays
Physical exam:
- Smaller stretched penile length in SGA cases
- Regardless of number of penile surgeries and height
- All had a normal timing and pace of puberty

Genetics
- No (likely) pathogenic monogenic variants (according to ACMG criteria)
- No diconic variant combinations (predicted as5%)-likely disease-causing) were withheld

Oligo-/azoospermia:
- 18.6% of hypospadias cases vs 4% of controls
- 59.1% of SGA cases
- 31.3% of AGA cases with complex hypospadias

Semen analysis
- Hormone levels as predictors of oligo-/azoospermia:
  - FSH: sensitivity 9.4%, specificity 100%
  - Inhibit B: sensitivity 21.9%, specificity 97.9%
  - ROC curve analysis: criterion FSH 4.11L/L; Inhibit B 196.4mg/L
  - Higher INS3 levels (p=0.042)

CONCLUSION
- All participants had a normal timing and pace of puberty
- Mainly subclinical hormone abnormalities
- Semen quality in AGA and complex hypospadias cases, especially in SGA and complex hypospadias cases
- No recurrent genetic causes were identified, no arguments for oligogenic effects

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FUNDING
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Participants
- Appropriate for gestational age (AGA)
- Smaller for gestational age (SGA)
- Distal hypospadias
- Midshaft hypospadias
- Proximal hypospadias
- Complex hypospadias
- Controls

- n=50

Adolescents & young adult men with hypospadias: Testicular function and in-depth genetic screening. Aims: To assess endocrine and reproductive outcome of young men born with hypospadias and explore genetic mechanisms underlying the development of hypospadias and eventual testicular dysfunction. INTRODUCTION: Background: Hypospadias affects approximately 1/200 newborn males and is sometimes included in the D50 spectrum. Few data currently support this hypothesis. Aims: To assess endocrine and reproductive outcome of young men born with hypospadias and explore genetic mechanisms underlying the development of hypospadias and eventual testicular dysfunction. METHODS: Study design: Cross-sectional study (Ghent and Vienna University Hospitals). Participants: Young adult men (16-21 years) born with non-syndromic hypospadias (n=193) and healthy male controls (n=50). Assessments: Physical exam, hormonal status (gonadotropins, androgens, insulin-like factor 3 (INSL3) & inhibit B), semen analysis and molecular genetic analysis (NGS-based panel of 474 genes & Oligogenic Resource for Variant Analysis (ORVAL)). RESULTS: Physical exam & hormone assays: Physical exam: Smaller stretched penile length in SGA cases, regardless of number of penile surgeries and height. All had a normal timing and pace of puberty. Genetics: No (likely) pathogenic monogenic variants (according to ACMG criteria). No diconic variant combinations (predicted as5%)-likely disease-causing) were withheld. Oligo-/azoospermia: 18.6% of hypospadias cases vs 4% of controls. 59.1% of SGA cases. 31.3% of AGA cases with complex hypospadias. Semen analysis: Hormone levels as predictors of oligo-/azoospermia: FSH: sensitivity 9.4%, specificity 100%; Inhibit B: sensitivity 21.9%, specificity 97.9%. ROC curve analysis: criterion FSH 4.11L/L; Inhibit B 196.4mg/L. Higher INS3 levels (p=0.042). CONCLUSION: All participants had a normal timing and pace of puberty. Mainly subclinical hormone abnormalities. Semen quality in AGA and complex hypospadias cases, especially in SGA and complex hypospadias cases. No recurrent genetic causes were identified, no arguments for oligogenic effects. Non-coding variants? Epigenetics? Placental insufficiency? Multifactorial?