Altered vascular function in boys with hypospadias—role of reactive oxygen species

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Introduction

- Hypogonadism, defined as clinical or biochemical evidence of low circulating testosterone, leading to abnormalities of the external genitalia occurs in approximately 1 in 300 live births.
- Animal models have demonstrated that there is a programming window during which androgens are required for normal masculinisation of the genital tract, without which hypospadias and other genital abnormalities occur.
- In recent years, multiple studies have demonstrated that low endogenous levels of testosterone increase the risk of cardiovascular morbidity and mortality in adult men. To date there is no data regarding this relationship in children.
- Here we determine if young boys with hypospadias, which are often associated with hypogonadism, exhibit vascular dysfunction through altered vascular androgen signaling, which may be ameliorated by testosterone.

Methods

We hypothesised that boys with hypospadias exhibit vascular dysfunction through altered vascular androgen signaling, which will be improved by testosterone.

Results

- Median (range) Hypospadias (n=20) Controls (n=29) p
  - Age 1.84 (1.3-6.4) yrs 2.0 (1.3-12.5) yrs 0.23
  - Gestation at birth 39 (35-40) wks 40 (26-42) wks 0.09
  - Birthweight 3.3 (0.7-4.0) kg 3.5 (1.5-6.6) kg 0.28
  - External maximisation score (EMCS) 10 (9-11) 12 (12-12) <0.0001
  - Proximal (50%) Mid (25%) Distal (45%)
  - Heart rate (bpm) 118 (90-155) 120 (70-168) 0.69
  - Systolic blood pressure (mmHg) 90 (75-100) 90 (70-105) 0.36
  - Diastolic blood pressure (mmHg) 40 (30-60) 45 (35-60) 0.27
  - Cholesterol (mmol/l) 4.4 (3.2-4.5) 4 (2.0-4.7) 0.44
  - Triglycerides (mmol/l) 1.1 (0.6-1.6) 0.8 (0.5-1.7) 0.09
  - Fasting glucose (mmol/l) 4.3 (3.4-5.3) 4.7 (3.5-6.8) 0.29
  - LH (range) (UI) 0.1 (0.1-1.4) 0.1 (0.1-0.5) 0.91
  - FSH (range) (UI) 0.7 (0.1-3) 0.5 (0.2-1.8) 0.61
  - Testosterone (nmol/l) <0.5 <0.5 >0.99
  - AMH (pmol/l) 875 (421-1472) 987 (371-1725) 0.98

Conclusions

- First study examining paediatric subcutaneous resistance arteries.
- Resistance arteries from boys with hypospadias are dysfunctional.
- Increased vascular contractility and reduced vasorelaxation may be due to increased ROS generation.
- Testosterone improves vasorelaxation but not contraction in hypospadias.

- Our findings indicate that hypogonadism is associated with vascular dysfunction and vascular oxidative stress in young boys. These phenomena may predispose boys with low testosterone levels to increased risk of cardiovascular disease later in life. Long-term studies are required to assess this.

Funding: British Heart Foundation Centre for Research Excellence Grant Number: RE/13/5/30177.