Pediatric Endocrinology

PEDIATRIC SEXUAL DIFFERENTIATION, PUBERTY, AND BONE BIOLOGY

Clitoromegaly in Premature Infants: Is It Truly Pathologic?

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Background: Normative data for clitoral size in premature infants are limited. Consequently, the potential for over-diagnosis is high; leading to unnecessary investigations, increased healthcare costs and parental stress. Several proposed mechanisms, e.g., persistence of fetal adrenal zone activity to term gestation, point to the transient physiologic nature of clitoromegaly in premature infants. Studies of normative data have shown a negative correlation between birth weight and clitoral size. We hypothesized that 1) the majority of clitoromegaly in premature infants is not associated with hormonal dysfunction and 2) lower birth weight and lower gestational age increase the likelihood of a formal consult in premature infants with perceived clitoromegaly. **Methods**: A retrospective chart review of female infants born at our institution from January 2012 to December 2018 with perceived clitoromegaly was conducted. Birth history, demographic and laboratory data were collected. Patients were divided into two groups: 'formal consult' and 'no formal consult' for clitoromegaly. True clitoromegaly was defined as clitoral length >9 mm or clitoral width >6 mm. Patients not meeting these criteria or those with clitoral edema, prominent clitoral hood were classified under false clitoromegaly. In the 'no formal consult' group, the documented discharge examination was used to assess persistence of clitoromegaly. Uni- and multi-variable logistic regression were used to determine factors that increased the likelihood of a formal consult. **Results**: 29 patients met inclusion criteria; 15 in the 'formal consult' group and 14 in the 'no formal consult' group. No significant differences were found between the groups in terms of birth weight, gestational age, race, ethnicity and maternal factors. History of IUGR (intrauterine growth restriction) was more common in the 'formal consult' group (60%) vs. 'no formal consult' group (21%) (p=0.04). Only 3/15 patients in the 'formal consult' group had true clitoromegaly; all 3 had normal 17-hydroxyprogesterone levels, and only 1 patient had transient elevation in androgen levels (androstenedione, deoxycortisol and testosterone). Of the 'no formal consult' group, only 3/14 patients had clitoromegaly noted on discharge; outcome was unknown for 1. Multi-variable logistic regression showed that lower gestational age (p=0.04) and history of IUGR (p=0.03), even after adjusting for birth weight, increased the likelihood of a formal consult. **Conclusion**: In summary, the majority of perceived clitoromegaly in premature infants is not associated with hormonal dysfunction. Lower gestational age and a history of IUGR increase the likelihood of a formal consult for clitoromegaly in these patients. Approximately half of the patients were noted to have false clitoromegaly indicating inconsistencies in examination technique and need for provider education.

Adipose Tissue, Appetite, and Obesity

ADIPOSE TISSUE BIOLOGY AND OBESITY II

Functional Characterisation of Human Heterozygous Non-Synonymous MC3R Variants

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Background: Melanocortin 3 receptor (MC3R) is a member of the melanocortin family of G-protein coupled receptors predominantly expressed in hypothalamic tissue. Rodent models have implicated MC3R in the pathogenesis of obesity, however in humans the relationship between obesity phenotypes and impaired MC3R function is less well established than that observed for loss of function mutations in the homologous MC4R.

Aim: Recently three heterozygous *MC3R* variants identified from candidate gene sequencing of an obese human cohort were reported to be pathogenic. We sought to functionally characterise the these *MC3R* non-synonymous variants (p.Q11X, p.I50T and p.A149V) *in vitro* and examine their associations to body mass index in an unselected population-based cohort.

Methodology: Functional characterisation of each variant was undertaken in HEK293 cells transiently overexpressing either wild-type MC3R or the respective MC3R mutant where cAMP-dependant luciferase activity in response to alpha-melanocyte stimulating hormone (α-MSH) was measured. Body mass index (BMI) was compared between heterozygous carriers of the MC3R variants of interest and control participants (matched for age and sex and ethnicity) identified within the UK Biobank whole exome sequencing dataset.

Results: Impairment of the canonical MC3R cAMP signalling response to α-MSH was observed for both p.Q11X and p.A149V MC3R variants when compared to wild-type MC3R receptor function *in vitro*. In contrast the cAMP signalling response of MC3R p.I50T to α-MSH was non-inferior to wild-type. Thirty-nine (male=18) heterozygous carriers of MC3R p.I50T were identified in the UK Biobank whole exome cohort. There was no statistical difference in median (IQR) BMI for female carriers 27.1(7.8) kg/m^2 vs. matched female control participants 26.2(5.5) kg/m^2 or male carriers 27.7(5.4) kg/m^2 vs. matched male control participants 27.4(4.9) kg/m^2. A single participant heterozygous for the MC3R p.Q11X variant (BMI= 28.3 kg/m^2) and two participants heterozygous for MC3R p.A149V (BMI= 24.7 and 25.1 kg/m^2 respectively) variant were identified in the UK Biobank whole exome cohort. BMI did not significantly differ from the match control population median for either of these variants.

Conclusion: *In vitro* assessment and phenotype correlates suggest that MC3R p.I50T is not an obesity causing mutation. Despite evidence of impaired receptor function *in vitro*, MC3R p.Q11X and p.A149V did not associate with obesity in this unselected population and further study are required to elucidate their pathogenicity in humans.