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# Pediatric Endocrinology

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## *Case Series of 16 Patients With 17β-Hydroxysteroid Dehydrogenase Type 3 Deficiency at Five Children's Hospitals in the United States*

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**Objectives:** The 17β-hydroxysteroid dehydrogenase type 3 (17βHSD3) enzyme, expressed in the testes, converts androstenedione to testosterone. Deficiency of 17βHSD3 causes a 46,XY difference of sex development (DSD). Until recently, just 12 cases of 17βHSD3 deficiency had been reported in the literature in the United States. We report a series of 16 patients diagnosed at five children's hospitals in the United States.

**Methods:** We performed a multi-center chart review of patients with 17βHSD3 deficiency diagnosed based on hormone values and/or sequencing and deletion/duplication analysis of the HSD17B3 gene.

**Results:** Sixteen patients were identified, ranging in age at diagnosis from birth to 22.3 years (average age 9.5 years). One patient, assigned female at birth, was diagnosed due to a positive family history of the condition. Three patients underwent testing due to discordance between the sex predicted by prenatal cell-free DNA testing and the external genital appearance on prenatal ultrasound or at birth (two were assigned female, one was assigned male). An additional four patients had non-binary (atypical) appearing external genitalia at birth (two assigned female, two assigned male). Two children assigned female at birth were diagnosed after undescended testes were identified during hernia repair in early childhood. Six patients who were assigned female at birth came to medical attention peri-pubertally due to signs of excess/undesired androgen effects and/or primary amenorrhea. Data on gender identity is limited by the current age of many of the patients, but as of most recent follow-up, one patient assigned male and one assigned female are reported to be

exploring their gender identities.

Four patients had a prior diagnosis of complete or partial androgen insensitivity syndrome and 8 had a prior diagnosis of 46,XY DSD of unknown etiology. Eleven patients had genetic testing confirming pathogenic or likely pathogenic variants in the HSD17B3 gene (two identified on whole exome, one on a DSD-specific multi-gene panel, and the remaining 8 on single gene testing). Of the patients without genetically confirmed 17βHSD3 deficiency, one had a clinical diagnosis due to a genetically-confirmed diagnosis in a sibling. The remaining four declined or have not completed genetic testing, but had hormonal testing consistent with the diagnosis.

**Conclusions:** 17βHSD3 deficiency is likely much more common in the US than previously appreciated, and can present at any age with a range of physical findings. Accurate diagnosis is important, as the broad category of 46,XY DSD encompasses a wide spectrum of gonadal malignancy risk, potential for pubertal hormone function and fertility, and gender identity outcomes. We suggest evaluating for this potential diagnosis with genetic and/or hormonal testing in cases of 46,XY DSD with absent uterus.

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