



## 2 Delayed Puberty in a 15-year-old Girl

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### PRESENTATION

A 15-year-old girl with a history of renal transplant at age 18 months due to presumed hemolytic uremic syndrome (HUS) presents for routine health supervision care. She is doing well overall. She complains of intermittent constipation. When asked about menarche, her mother states that the patient has not yet had a period and notes that she has had minimal breast development.

Regarding her medical history, she was born at term after a normal prenatal course, uncomplicated delivery, and nursery course. Physical examination findings at birth were normal, including normal external female genitalia. At 5 months of age she developed an acute diarrheal illness with fever and vomiting and was hospitalized for 1 week. One month later, at 6 months of age, she was readmitted with renal failure, anemia, and hypertension and was clinically diagnosed as having HUS. At 12 months of age she underwent bilateral nephrectomies for end-stage renal disease and malignant hypertension. At 18 months of age she received a living donor kidney transplant, which has functioned well for 15 years.

There was no known family history of kidney disease, menstrual abnormalities, infertility, polycystic ovary syndrome, premature ovarian failure, thyroid disease, or other autoimmune disease. Her mother reports that both parents had normal pubertal timing, with her mother having menarche at age 12 years. Midparental height is at the 25th percentile.

At the time of her 15-year health supervision visit, her home medications include tacrolimus, mycophenolate mofetil, low-dose alternate-day prednisone (2 mg), lisinopril, and cholecalciferol.

On physical examination her height is 5'4" (55th percentile), weight is 55.2 kg (60th percentile), and BMI is 20.8 (59th percentile). Height percentile is slightly increased from previous values (Fig 1). Abdominal examination reveals a well-healed midline abdominal surgical scar with allograft felt on deep palpation to the right of midline in her lower abdomen and no additional masses. Pubertal assessment reveals Tanner stage 1 breast development and Tanner stage 3 pubic hair. Genitourinary examination demonstrates normal prepubertal female genitalia. There was no clitoromegaly and no posterior labial fusion, and the vaginal mucosa was nonestrogenized.

**AUTHOR DISCLOSURE** Drs Hughes, Mendley, Cooke, Malone, and Beckwith-Fickas have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

## 2 to 20 years: Girls Stature-for-age and Weight-for-age percentiles

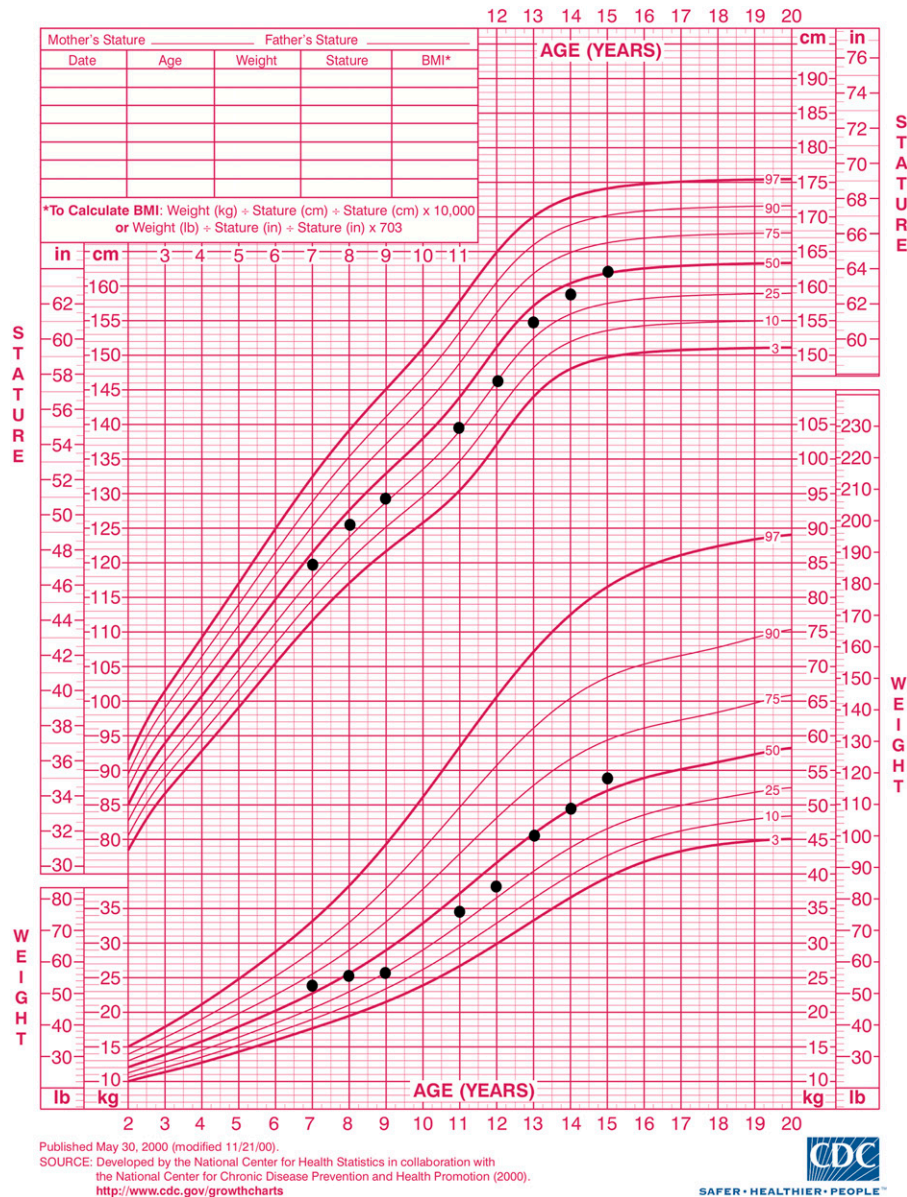


Figure 1. Growth chart. Stature for age and weight for age, ages 7 through 15 years.

## DISCUSSION

### Differential Diagnosis

Delayed puberty is defined in females by the absence of breast development at 13 years of age or primary amenorrhea at 15 years of age. (1)(2) Although this patient did have pubic hair development, she was found to have no breast development (Tanner stage 1) and primary amenorrhea at 15 years old consistent with pubertal delay.

The differential diagnosis of delayed puberty is very broad and can be divided into 2 main categories: primary

and secondary hypogonadism. Primary, or hypergonadotropic, hypogonadism is identified by elevated gonadotropin levels (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) in the setting of low or prepubertal levels of sex steroids (elevated gonadotropin mean levels above the upper limit of the adult reference range). This category can be further subdivided into congenital (eg, chromosomal abnormalities) or acquired (eg, autoimmune, postinfectious, surgery, trauma, chemotherapy, or radiotherapy) causes. Secondary, or hypogonadotropic, hypogonadism is defined as low or normal LH and FSH levels (below the

upper limit of the adult reference range) with prepubertal estrogen or testosterone levels. This category also subdivides into acquired causes (acquired hypopituitarism, “functional” gonadotropin-releasing hormone deficiency such as constitutional delay of growth and puberty, chronic illness, malnutrition, etc) and congenital causes (idiopathic hypogonadotropic hypogonadism, gonadotropin-releasing hormone deficiency associated with mental retardation and obesity syndromes, and congenital brain malformations).

Comprehensive history and physical examination is the first step to narrowing the differential diagnosis. Initial testing includes gonadotropin and sex hormone levels, prolactin, thyroid function tests (thyrotropin and free T<sub>4</sub>), and bone age radiographs. (1)(2)(3) Some children may require testing for nutritional disorders and systemic illness, such as a complete blood cell count, comprehensive metabolic panel, inflammatory markers, and testing for celiac disease. Initial gonadotropin and sex hormone levels may suggest hypergonadotropic (high FSH/LH levels) versus hypogonadotropic (low FSH/LH levels) hypogonadism, leading to other targeted testing (eg, karyotype, brain imaging).

In this patient, her history was notable for renal failure at 6 months of age, bilateral nephrectomies at 12 months of age, and living donor kidney transplant at 18 months of age. After kidney transplant, immunosuppressive agents were used. Her history was negative for use of agents linked to toxin-induced ovarian failure.

Delayed puberty is common in children with a history of renal failure and delayed transplant, as well as in children with poor graft function and high glucocorticoid exposure. (4) Fortunately, our patient had done well, with a short period on dialysis before transplant and a posttransplant period with a rapid steroid taper. In patients with end-stage kidney disease, early transplant and minimal steroid use allows for normal pubertal development in most patients. (4) Family history was noncontributory in this patient. There was no clinical concern for undiagnosed chronic disease or malnutrition. LH and FSH levels were obtained and found to be significantly elevated, with a near prepubertal estrogen level. The results indicated primary (hypergonadotropic) hypogonadism, and, therefore, a karyotype was obtained to rule out a chromosomal abnormality. The karyotype result was 46 X,Y. This confirmed a disorder of sexual development with 46 X,Y complete gonadal dysgenesis.

## Diagnosis

This case was particularly humbling because it showed that our original diagnosis was incorrect and we waited almost 15 years for the correct one. We had presumed that renal failure

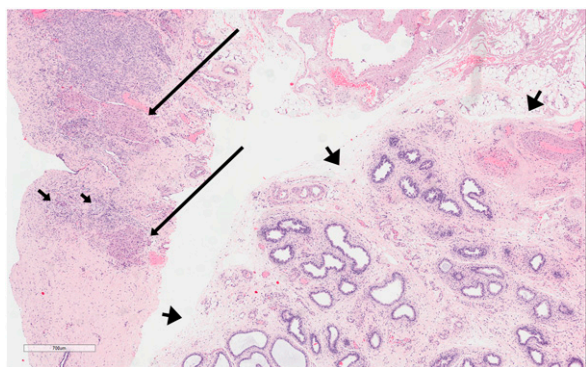
after a diarrheal illness in this infant was due to HUS, although an infectious source was never identified, and laboratory features were inconclusive. There were never signs of a recrudescence of HUS after end-stage renal disease. Her course on peritoneal dialysis included severe hypertension, and bilateral nephrectomies were performed. The histologic analysis of her kidneys (largely glomerulosclerosis) was not diagnostic of an initial cause for renal failure but did not suggest remote HUS. However, the renal pathology was notable for large clusters of immature cells, which were described as nephrogenic rests in the pathology report.

The patient's X,Y karyotype led to an appropriate concern for a mutation of the *WT1* gene. Genetic testing was performed and demonstrated a *de novo* pathogenic *WT1* mutation, c.1384 C>T, consistent with Denys-Drash syndrome. *WT1* is a zinc-fingered DNA binding protein that can act as a transcriptional activator or repressor, depending on the context. Based on the patient's clinical course and *WT1* mutation we can confidently assign her the diagnosis of Denys-Drash syndrome. Although initially the syndrome was a clinical observation of patients with ambiguous genitalia and nephrotic syndrome, our understanding has expanded with discovery of the *WT1* gene (in Wilms tumor) and the recognition of *WT1* expression in the developing kidney, gonads, and external genitalia. Denys-Drash syndrome is quite rare, with approximately 150 reported individuals in the scientific literature, yet the full spectrum of the disease is being redefined in an era where *WT1* gene testing is available. (5) One can speculate that other genes involved in genitourinary development may also be causative.

We are highly suspicious that the clusters of immature cells (nephrogenic rests) found in the kidney when the patient was age 1 year were the result of the *WT1* mutation, and she was at extremely high risk for Wilms tumor, which was avoided. In hindsight, we realize how fortunate it was that we performed bilateral nephrectomies before immunosuppression, but must admit to luck rather than skill in this decision.

## Management

The approach to disclosure of 46 X,Y karyotype to this female patient and her family was carefully considered. When we disclosed the diagnosis, we attempted to have both parents and the patient present together, but only the mother and patient were able to attend the clinic visit. All initial disclosure was given to the mother and patient simultaneously and presented by 2 physicians who had prepared extensively before meeting with the family. This patient identified as female and care was taken to ensure that we always addressed the patient as a female individual



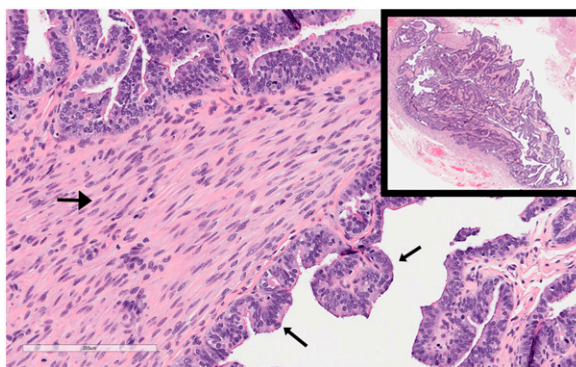
**Figure 2.** Streak gonads. There are testicular remnants with fibrosis (wide arrows), areas of Leydig cells (long arrows), and Sertoli cell-only seminiferous tubules (short arrows).

who had an X,Y karyotype. Flexibility, empathy, and an individualized approach were used and are required in these situations. Ideally a multidisciplinary team, including primary care, endocrinology, surgery, social work, and psychiatry, should be involved to support the family. (6)

Magnetic resonance imaging of the pelvis was completed and notable for streak gonads and an apparently normal prepubertal uterus.

Once the appropriate genetic and clinical diagnosis was made we recognized that the patient was at risk for malignancy in her streak gonads, and surgical removal was planned. Histologically, the streak gonads demonstrated features of testicular development (Fig 2 demonstrating seminiferous tubules, Leydig cells) as well as Mullerian duct remnants (Fig 3). Her operative course was complicated by injury to her transplanted ureter with transient obstructive acute kidney injury in the renal allograft. The transplant ureter was repaired and anastomosed to her remaining native ureter with resolution of acute kidney injury and subsequent good allograft function.

This patient strongly desired normal breast development similar to her peers and was happy to comply with medical induction of puberty. Our treatment plan included initiation of an estrogen patch, with a slow increase to replicate natural puberty progression and development of secondary sexual characteristics. Oral or patch forms of estrogen can be used; however, recent evidence suggests superiority of



**Figure 3.** Streak gonads. The contralateral side shows fallopian tube-like tissues (low power, inset). These areas consist of ciliated epithelium (thin arrows) lining fibroconnective tissue with smooth muscle proliferation (wide arrow).

topical estrogen patches due to decreased liver estrogen exposure and the possibility of fewer adverse effects and superior breast development. (7)(8) A progestin was added after breakthrough bleeding developed. (6) Fertility options, including adoption and use of an egg donor with reproductive endocrinology to help sustain pregnancy, were discussed.

### Lessons for the Clinician

- This case highlights the importance of regular pubertal examinations and separately tracking both the timing of gonadarche (breast/testicular development) and pubarche (pubic hair development).
- We discuss how to approach the differential diagnosis of delayed puberty, including the 2 main categories of primary (hypergonadotropic) hypogonadism and secondary (hypogonadotropic) hypogonadism.
- Care should be taken when approaching discussions of disorders of sexual development with families.
- We highlight a rare genetic condition, Denys-Drash syndrome, which in retrospect explained the renal failure that this patient developed in infancy.

*References for this article are at <http://pedsinreview.aappublications.org/content/41/9/485>.*



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## Case 2: Delayed Puberty in a 15-year-old Girl

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