A 16-Year-Old Girl with Amenorrhea

Robert Listernick, MD

This 16-year-old girl was seen for evaluation of primary amenorrhea. She had developed breast tissue and pubic hair starting at 11 years of age but had yet to start her menses. Otherwise, she was totally asymptomatic. Her medical history was unremarkable. Her family history was unremarkable. Her mother is 5’1” and had menarche at age 11 years. Her father is 5’7” and had normal timing of puberty.

On exam, she was an alert, healthy-appearing teenager. Her weight was in the 80th percentile and height in the 70th percentile. Vital signs were unremarkable. Her general exam was normal. Her breasts were Tanner stage 3 bilaterally. Her pubic hair was Tanner stage 4. There was no clitoromegaly and no posterior labial fusion.

Robert Listernick, MD, moderator: How should one approach the evaluation of primary amenorrhea?

Britt Allen, MD, general academic pediatrician: First we should define our terminology. Primary amenorrhea is defined as the absence of menarche at the age of 15 years in the presence of secondary sex characteristics and normal growth. Another definition in the literature is the absence of menarche 3 years after the development of breast buds. As to etiology, I like to approach the differential diagnosis based on the anatomic level of dysfunction. First, hypothalamic and pituitary function may be abnormal primarily or due to infiltrative diseases, so the gonadotropins, luteinizing hormone (LH), and follicle stimulating hormone (FSH) should be measured. In addition, hypothroidism and hyperprolactinemia can each cause primary amenorrhea. Moving down the axis, ovarian etiologies such as gonadal dysgenesis, Turner syndrome, or polycystic ovary syndrome should be considered. Finally, anatomic abnormalities of the uterus and vagina, such as imperforate hymen, are part of the differential diagnosis.

Dr. Listernick: Obviously we’re just scratching the surface of the many causes, but are there systemic diseases that should be considered?

Dr. Allen: A variety of enzyme and receptor abnormalities can lead to primary amenorrhea. Examples include 5-alpha-reductase deficiency in which a 46,XY individual appears as a normal female or as one with ambiguous genitalia at birth only to become virilized in adolescence due to an inability to convert testosterone to dihydrotestosterone, and complete androgen insensitivity syndrome due to defects in the androgen receptor. These XY babies look like normal girls but lack all Mullerian structures — fallopian tubes, uterus, and upper third of vagina. Of course, we shouldn’t forget about eating disorders, which often cause secondary amenorrhea but may result in primary amenorrhea as well.

Dr. Listernick: Great. Moving on, the following tests were normal: prolactin, estradiol, beta-HCG, anti-Mullerian hormone, thyroxine, TSH, dehydroepiandrosterone (DHEAS). LH and FSH were both markedly elevated, being in the pubertal range. Testosterone was elevated for a female. Can you walk us through these results?

Courtney Finlayson, MD, pediatric endocrinologist: The gonadotropins are markedly elevated; rather than saying they were necessarily in the pubertal range, I would suggest that they are actually in the range seen in menopause or gonadal failure. The estradiol is lower than I would expect for a girl who has Tanner 3 breast development. The testosterone is higher than expected for a female.

Dr. Listernick: Your initial gestalt?

Dr. Finlayson: This child has hypergonadotropic hypogonadism and her primary amenorrhea is due to primary gonadal failure.

Dr. Listernick: I forgot to mention that her karyotype is 46,XY.

Dr. Finlayson: That changes things a bit! She has a 46,XY disorder of sex development. There are three main categories of these disorders — disorders of gonadal development, disorders of androgen synthesis or action, and the “other” category. Thinking it through a bit, this girl has no signs of excess virilization (excess androgens). Coupled with our knowledge from the laboratory testing that she has gonadal failure, this suggests that she has a 46,XY disorder of sex development due to a disorder of gonadal development.
Firm Rounds

Dr. Listernick: Tell us a bit about sex development.

Dr. Finlayson: First, chromosomal sex is determined in which the fetus is either XX or XY. Next, if the fetus is XY, the testes-determining genes on the Y chromosome, the first being SRY, activate a number of transcription factors that determine whether the gonad becomes a testis.

Dr. Listernick: And in this girl?

Dr. Finlayson: We know that she has gonadal failure; her gonads could be testes or ovotestes that don’t work properly or they could be ovaries. We also know that this is not a normal testis because of the low levels of anti-Mullerian hormone. Normal testes make high levels of anti-Mullerian hormone that causes regression of the Mullerian structures. We should look at the imaging.

Jennifer Nicholas, MD, pediatric radiologist: The first test she had was a transabdominal ultrasound. There appears to be a small uterus, but the most prominent finding is a heterogeneous right adnexal mass with a few calcifications. Without the history, you would think that this was a dermoid cyst or teratoma. It’s hard to clearly separate the mass from a right ovary and I don’t see a definite left ovary. Computed tomography better defined the mass and the uterus but didn’t give us much more useful information.

Dr. Listernick: How does this help us identify the underlying disorder?

Dr. Finlayson: As I previously mentioned, this is not a normal testis as it did not produce enough anti-Mullerian hormone to cause regression of the uterus and the upper portion of the vagina. The external genitalia are completely normal, indicating that there wasn’t adequate testosterone during development to cause their virilization. For the moment, I can only summarize that she has 46,XY disorder of sexual development caused by a disorder of gonadal development.

Dr. Listernick: Forgetting about the mass for the moment, how will we take care of her?

Joel Frader, MD, pediatric ethicist: Fortunately, we are starting a multidisciplinary clinic for the care of children with disorders of sex development (DSD). There are essentially two groups of children whom we will see: 1) those who are genetically and phenotypically male or female but who within their own mindset have gender dysphoria, and 2) children born with either ambiguous genitalia or genitalia that don’t match up with the chromosomal sex. Obviously, a multitude of physicians need to be involved, including specialists from endocrinology, general surgery, urology, psychiatry, and ethics.

Dr. Listernick: If this girl were coming to your clinic for the first time and you had all this information beforehand, how would you approach the conversation?

Dr. Finlayson: Obviously, there’s no one standard way to have this conversation. I start out acknowledging that she is a girl but that she has chromosomes that are more typical for a boy. I generally explain how development works and show them pictures of how every fetus starts out female and how the internal organs and genitalia develop. I think it’s very useful for families to understand that girls and boys start out the same and that very few factors make the difference in terms of development into what we typically think of as a girl or boy.

Catherine Hunter, MD, pediatric surgeon: I was the first physician to see her at our institution and, incredibly, she had been told that by her previous physicians that “she was a boy”; or at least that’s what she and the family heard. So, the first thing I stated was that unequivocally she was 100% girl and everybody started crying!

Jill Weissberg-Benchell, PhD, child psychologist: As we see in this case, it’s extremely important to get the family’s story before you start educating them. We need to hear what the family understands about what they’ve been told and how they are feeling about the information they’ve already received. It’s also important to hear about how the family has experienced the medical care system up to this point. All of these areas are important to assess before we offer our opinions or thoughts. I spoke with them after they heard that she was, indeed, a girl. I felt that she was one of the most normal, well-adjusted teenagers I have ever met to the point where she said: “So, the bottom line here is that I will probably need to take a pill a day and I might not be able to have babies the typical way of having babies, which some women can’t do anyway. I’m OK with that.”

Elizabeth Yerkes, MD, pediatric urologist: I find that the most difficult discussions I have relate to newborns with ambiguous genitalia, in whom it may take weeks to figure out what to recommend, as well as teenagers who seem to have a normal gender identity but who have had a change in the appearance of their genitalia during puberty. They just want to know, “Am I a boy or am I a girl and what are you going to do about it?” It’s extremely important for the

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Key Learning Points

1. Primary amenorrhea is defined as the absence of menarche at the age of 15 years in the presence of secondary sex characteristics and normal growth.

2. Markedly elevated gonadotropins in the presence of low sex hormones are the hallmarks of hypergonadotropic hypogonadism and primary gonadal failure.

3. 46,XY disorders of sex development are primarily due to either disorders of gonadal development or disorders of androgen synthesis or action.

4. Gonadoblastoma is a benign tumor that generally arises from dysgenetic gonads. Almost always the patient is either XY or has detectable Y chromosome genetic material.

5. Dysgerminomas, which are malignant, may be seen in children who have dysplastic gonads.
physician to be able to say upfront “I don’t know” rather than give out misinformation.  

Dr. Listernick: Going back to the comment the patient made earlier about pregnancy, is she likely to be fertile?

Dr. Finlayson: I doubt it. She has a very small uterus, and the combination of high gonadotropins and low estradiol suggest she has gonadal failure. She will need estrogen replacement therapy to continue puberty and for bone health.

Dr. Listernick: What about her gonads?

Dr. Finlayson: In any child who has gonadal dysgenesis (assuming that’s her diagnosis), you have to consider removal of the gonads due to an increased risk of malignancy. Different DSDs have different risks. She most likely has Swyer syndrome, which is a heterogeneous group of disorders of 46,XY individuals with gonadal dysgenesis. This includes children who have mutations in the SRY gene or any number of transcription factors. Their risk of developing a malignancy is over 30%, gonadoblastoma being the most common tumor. Whenever we see these children as infants, we recommend removal of the gonads.

Dr. Listernick: So she was actually initially referred to Dr. Hunter because of the adnexal mass.

Dr. Hunter: On the diagnostic laparoscopy, the uterus appeared smaller than normal. There was a very small “streak gonad” on the left. I removed a bi-lobed mass on the right that was attached to the fallopian tube. There was no omental studding or evidence of peritoneal tumor spillage. I couldn’t see a definite right-sided gonad.

Nitin Wadhwani, MD, pediatric pathologist: Grossly, the mass is bi-lobed; one side is tan and gelatinous while the other has a grittier, calcified appearance. Microscopically, the former area has groups of abnormal cells with lots of clear cytoplasm and prominent nucleoli forming nodules; this area is a dysgerminoma. The latter area with calcifications is a gonadoblastoma. Basically, we have a dysplastic ovary with dysgerminoma arising within a gonadoblastoma. The left-sided “streak gonad” is ovarian stroma without ova or seminiferous tubules.

Dr. Listernick: This must have been an incredibly difficult first visit having to deal with both the DSD issue and the concern for malignancy at the same time.

Dr. Frader: It’s important to remember what we discussed earlier — you need to be clear and transparent. If you either omit an important piece of information or give misinformation, you run the risk of losing their trust.

Dr. Listernick: Can we define our terms as to these different tumors?

Elaine Morgan, MD, pediatric oncologist: Gonadoblastoma is a benign tumor that generally arises from dysgenetic gonads. Almost always the patient is either XY or has detectable Y chromosome genetic material, either 46,XY or 45,XO/46,XY.

Dr. Finlayson: A small percentage of girls with Turner syndrome have detectable portions of the Y chromosome. They have as high as a 40% chance of developing gonadoblastoma.

Dr. Listernick: And dysgerminoma?

Dr. Morgan: As Dr. Wadhwni pointed out, the two tumors look quite different macroscopically. Dysgerminomas are true malignancies. Although most commonly seen in normal adult women, there is a clear association with gonadoblastomas in children with dysplastic gonads. She will need a metastatic work-up, including an evaluation of local lymph nodes; although I would perform a CT scan of the chest and abdomen, these tumors rarely metastasize to the liver. If this is a stage I tumor, there is evidence that surgical resection can be the only therapy. For higher stage tumors, a short course of chemotherapy is generally given.

Dr. Hunter: We also have to repeat surgery and remove the fallopian tube on that side in children who have dysgerminomas.

Dr. Finlayson: Her genetic evaluation is ongoing. I definitely want to see if we can molecularly identify a mutation in SRY.

Dr. Listernick: Thank you, everyone.