A Well-Appearing 5-Year-Old Girl with Heart Murmur and Hypertension

Robert Listernick, MD

A 5-year-old girl was referred to a cardiologist for evaluation of a murmur and hypertension noted during a well-child visit. There was no history of chest pain, dyspnea, palpitation, dizziness, syncope, poor exercise tolerance, or easy fatigability. She participates in physical activity and keeps up with her peers. Review of systems and medical history were negative.

On examination, she was a well-appearing girl in no distress. Her vital signs included pulse of 105 beats per minute, respiratory rate of 28 breaths per minute, and blood pressure of 110/68 mm Hg, which was at the 95th percentile for her age. Weight and height were both at the 50th percentile. Quoting from her chart: "she had somewhat distinct facial features, suspicious of genetic syndrome." Lungs were clear. There was a normal precordial impulse with normal rate and rhythm. All pulses were normal. S1 and S2 were normal with physiologic splitting. There was a grade II/VI early systolic ejection-type murmur heard at the left upper sternal border radiating into the back. There was no hepatosplenomegaly. She had normal genitalia. Neurologic examination was entirely normal.

Electrocardiogram was normal. Echocardiogram showed trivial supravalvar aortic stenosis and peripheral pulmonary branch stenosis. There was no ventricular hypertrophy.

Robert Listernick, MD, moderator: I assume that she initially was referred to the cardiologist because of concerns for the presence of a coarctation of the aorta. Aren't they all identified in the neonatal period?

Elfriede Pahl, MD, pediatric cardiologist: Unfortunately they are missed quite often. Several times yearly, I see teenagers who have hypertension with previously undiagnosed coarctations.

Dr. Listernick: Is echocardiography 100% sensitive for detecting them?

Dr. Pahl: Unfortunately not, particularly when they are low in the thoracic descending aorta. In addition, acoustic windows are not as good in older children who have thicker chest walls, which may lead to the occasional false-negative study. We often use magnetic resonance imaging to identify these lesions in older patients. I have never seen this patient but it sounds like a classic murmur of peripheral branch pulmonary artery stenosis.

Dr. Listernick: What do you think about the "trivial supravalvar aortic stenosis"?

Dr. Pahl: Functionally, not much. But I'm sure the cardiologist was wondering about the possibility of Williams syndrome given the "dysmorphic" facies.

Joel Charrow, MD, geneticist: Williams syndrome is an example of a contiguous gene deletion syndrome involving the Williams-Beuren syndrome critical region on chromosome 7. The clinical manifestations are variable depending on the size of the deletion. Loss of the elastin gene within this region is specifically associated with connective tissue abnormalities in any arterial vessel, most notably the development of supravalvar aortic stenosis in as many as 89% of the children.

Dr. Listernick: What are the other manifestations of Williams syndrome?

Dr. Charrow: They're myriad. In brief, they are described as having "elfin facies" (although I've never seen an elf), mild cognitive disabilities, a distinctive "loquacious personality," infantile hypercalcemia, and a number of other end organ problems.

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Dr. Listernick: Can the hypertension be part of Williams syndrome?

Dr. Pahl: An unusual physical finding is due to the Coanda effect, which is described as the tendency of a fluid jet to be attracted to a nearby surface. The jet caused by the supravalvar aortic stenosis is oriented to the right arm and may lead to higher blood pressures in the right arm as compared to those in the left arm.

Dr. Listernick: If Williams syndrome is suspected, what is the appropriate test?

Dr. Charrow: If one has a high suspicion for Williams syndrome, the cost-effective test would be fluorescent in situ hybridization (FISH) for the Williams syndrome critical region.

Dr. Listernick: She was next referred to Dr. Bock for management of hypertension, who started her on amlodipine.

Margret Bock, MD, pediatric kidney diseases physician: Her blood pressure was borderline elevated and she had normal kidney function. I performed a urinalysis looking for the presence of hematuria or proteinuria as might be seen in glomerulonephritis. In addition, I ordered a renal ultrasound to make sure she had structurally normal kidneys. Although I also ordered Doppler imaging to assess for the presence of renovascular hypertension, we are aware that this is not a particularly sensitive test. Finally, her thyroid profile and complement levels were normal, as were the results of the other tests.

Dr. Listernick: Can you comment on your choice of antihypertensive therapy?

Dr. Bock: There is no recommendation in pediatrics as to the first-line antihypertensive agent. In adults, it still is a thiazide. In children, we generally start with either a calcium channel blocker, angiotensin-converting-enzyme (ACE) inhibitor or angiotensin II receptor antagonist, also known as an angiotensin receptor blocker (ARB). ACE inhibitors and ARBs are especially good for children who have essential hypertension secondary to either body habitus or a family history. Given the clinical suspicion for Williams syndrome, I chose amlodipine for this patient because these children are prone to developing hypercalcemia in the first year of life. Her body mass index was normal.

Dr. Listernick: And what did you think about her possible dysmorphic facies?

Dr. Bock: As has been stated, I felt that she looked distinctly different than her parents.

Dr. Listernick: Dr. Charrow was not the geneticist who saw her. So, here's a relatively broad question. Can you help us understand when a physician should order FISH testing for a specific syndrome versus either a microarray versus a traditional chromosomal karyotype?

Dr. Charrow: That's tough to answer without being especially long-winded! In brief, pediatricians should order FISH testing when they have a specific hypothesis involving a well-described, clinically suspected microdeletion syndrome; in this case, Williams syndrome. Absent that, as in most children we see for evaluation of intellectual disability of unknown cause or multiple congenital anomalies, I would recommend microarray because it detects microdeletions and small duplications that would not be visible on routine chromosome analysis.

Dr. Listernick: And the value of routine karyotype testing?

Dr. Charrow: I order that only when I suspect an easily recognizable chromosomal syndrome such as trisomy 21 or 18.

Dr. Listernick: So she had a microarray ordered. I'll quote directly from the report. "A hybridization pattern consistent with an XY sex chromosome complement was observed and has subsequently been confirmed by chromosome analysis. The karyotype was 46XY; from an apparently female patient this is an abnormal finding and is consistent with sex reversal. The basis for sex reversal in this patient is not apparent from either the microarray or the karyotype analysis. Genetic counseling is recommended." Hard to disagree with that last sentence! She was immediately referred to Dr. Finlayson. She is the endocrinologist for the Gender and Sex Development program. Did you feel she looked dysmorphic when you finally saw her?

Courtney Finlayson, MD, pediatric endocrinologist: I agree that she didn't look like her parents; she had mildly coarse facial features with a prominent mandible. Our Gender and Sex Development program has two arms—the Gender and Development program for children who have gender nonconformity, such as those who might be transgender, and the Sex Development program for children who have disorders of sex development, such as this patient. Many specialties are represented in the program, including endocrinology, urology, pediatric surgery, psychology, psychiatry, and adolescent medicine.

Dr. Listernick: How can you explain her findings including the hypertension and the XY karyotype?

Dr. Finlayson: She has a very rare type of congenital adrenal hyperplasia, not 21-hydroxylase deficiency, which is on most newborn screening panels. She has a mutation in the P450c17 enzyme that codes for two enzymes,

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17-hydroxylase and 17,20 lyase. The end result is overproduction of the mineralocorticoids 11-deoxycorticosterone and corticosterone, leading to hypertension. Aldosterone levels are low because of suppression of the renin-aldosterone-angiotensin pathway. In addition, she has underproduction of androgens. Although patients with 17-hydroxylase deficiency have decreased levels of cortisol, they don't develop life-threatening adrenal insufficiency because of elevations of corticosterone and other glucocorticoids.

Dr. Listernick: Can you walk us through why she has perfectly normal external female genitalia?

Dr. Finlayson: This child is XY. In brief, the Y chromosome encodes for certain transcription factors that tell the gonad how to develop, such as the *SRY* gene, which codes for a protein called the sex-determining region Y protein. This protein is a transcription factor that dictates that the undifferentiated gonad should become a testis. The differentiated testis produces Mullerian-inhibiting substance, which causes regression of Mullerian structures, including the uterus, the fallopian tubes, and the upper portion of the vagina. The testes also make testosterone, which causes stabilization of the internal male structures including the Wolffian ducts, vas deferens, and seminal vesicles. Lack of production of testosterone leads to absent dihydrotestosterone, which is ultimately responsible for fusion of the labial-scrotal folds and growth of the phallus. Hence, these children have perfectly normal female external genitalia.

Dr. Listernick: Her pelvic ultrasound didn't show any Mullerian structures as expected. However, it also didn't identify any gonads. Once identified, do her testes have to be removed because of the risk of future malignancy?

Dr. Finlayson: Good question. In many children with XY disorders of sexual development, there is a real risk for the development of gonadoblastoma in the undescended testes. However, there are very little data in this specific disorder. Given that her gonads are likely normal testes, the risk may be small, as seen in boys with cryptorchidism. I'm not yet sure what I'll recommend.

Dr. Listernick: Treatment?

Dr. Finlayson: The medical part is easy. Hydrocortisone will feedback on the hypothalamus and suppress the overproduction of mineralocorticoid.

Dr. Listernick: Now the hard part. What do you tell the child and the family?

Dr. Finlayson: First, I take a great deal of time to explain the typical process of sex development and all the steps that have to go exactly the right way for us to develop into typical males or females. I'm very careful with my word choice. For instance, I might say, "this is what somebody might think of as a typical male or a typical female, but there are a lot of variations that most people have never heard of, not because they don't exist because people don't talk about them very much."

Dr. Listernick: You must get the question, "Well, is she a girl or is she a boy?"

Dr. Finlayson: Occasionally. We respond carefully, with the psychologists saying something like "She's the same little girl that she was before coming here. Nothing about her has changed. We just understand a bit more about how her body developed."

Dr. Listernick: Given her underlying metabolic defect, is there any reason to believe that her ultimate gender identity will be anything other than female?

Dr. Finlayson: We don't really have a very good understanding of how hormones affect gender identity. We know that hormones affect gender behavior and gender roles. For example, girls with typical 21-hydroxylase deficiency often will display "tomboyish" behavior. They may play with trucks and tend to go into careers that are typically thought of as more "male." However, 95% of them will have a female gender identity.

Panelists

Robert Listernick, MD
Moderator

Elfriede Pahl, MD
Pediatric cardiologist

Joel Charrow, MD
Geneticist

Margret Bock, MD
Pediatric kidney diseases physician

Courtney Finlayson, MD
Pediatric endocrinologist

All panelists practice at the Ann & Robert H. Lurie Children's Hospital of Chicago, IL, where this discussion, part of a weekly series, was recorded and transcribed for *Pediatric Annals*.

Key Learning Points

1. Williams syndrome is an example of a contiguous gene deletion syndrome involving the Williams-Beuren syndrome critical region on chromosome 7. The clinical manifestations are variable depending on the size of the deletion and include "elfin facies," mild cognitive disabilities, a distinctive "loquacious personality," infantile hypercalcemia, and supravalvar aortic stenosis.
2. Pediatricians should order fluorescent in situ hybridization testing when they have a specific hypothesis involving a well-described, clinically suspected microdeletion syndrome such as Williams syndrome.
3. For evaluation of children who have intellectual disability or multiple congenital anomalies of unknown cause, microarray is useful because it detects microdeletions and small duplications that would not be visible on routine chromosome analysis.
4. The *SRY* gene on the Y chromosome is responsible for the production of the transcription factor sex-determining region Y protein, which dictates that the undifferentiated gonad should become a testis.
5. The differentiated testis produces Mullerian-inhibiting substance, which causes regression of Mullerian structures including the uterus, the fallopian tubes, and the upper portion of the vagina. The testes also make testosterone, which causes stabilization of the internal male structures including the Wolffian ducts, vas deferens, and seminal vesicles.

Dr. Listernick: What do you tell the child?

Dr. Finlayson: Thus far, most of this discussion has happened with the child in the waiting room. We're extremely careful in what we say to the child. At this age, we don't need to say anything. However, this diagnosis is often made in teenagers who seek medical attention due to primary amenorrhea. First, I try to sort out how much information the family may have already shared with the patient and how they might like us to approach the discussion. A 15-year-old girl should be given this information but often we first discuss it with the parents and then with the parents and the child.

Dr. Listernick: What about puberty and pregnancy?

Dr. Finlayson: She will need hormonal support to induce puberty as well as thereafter. She's not going to be fertile in any typical way as she has no internal female organs. However, our program is working on fertility preservation in patients with disorders of sexual development. Theoretically, if she has any germ cells in her gonads they could be allowed to mature and be preserved in a laboratory.

Dr. Listernick: In addition, her parents will need genetic counseling regarding future pregnancies as this is an autosomal recessive disorder. Thank you, everyone.