A 14-Year-Old Girl with Leg Length Discrepancy

Robert Listernick, MD

A 14-year-old girl was referred for evaluation of leg length discrepancy. It had been noted around 6 years of age but no consultation had been sought. During her recent growth spurt, the discrepancy was noted to have increased with her right leg longer and she sometimes walked abnormally. At the end of the day, she often would have thigh pain, which seemed to be related to the level of activity. Her past medical history was unremarkable, apparently.

On exam, she was 5’6” tall with a body mass index (BMI) in the 25th percentile. Her spine was straight. Her hips showed full flexion and extension with 70° of abduction bilaterally. Her right hip had 30° of internal rotation and 40° of external rotation compared with 45° and 65° on the left side. She had tight hamstrings on the left. Measurements from the anterior superior iliac spine to the medial malleolus demonstrated a difference of 1.9 cm, the right side being longer. She had a positive Galeazzi and positive Allis test. The right leg was circumferentially larger at both the thigh and the calf. Standing AP X-ray demonstrated a 1.9 cm leg length discrepancy. A 1 cm lift in her shoe was prescribed, which helped both her thigh pain and her gait.

**Robert Listernick, MD, moderator:** How does a leg length discrepancy come to medical attention?

**John Grayhack, MD, pediatric orthopedic surgeon:** Often, the parent notices an asymmetry of stance. Although it’s generally well tolerated, leg length discrepancy might lead to thigh or hip pain in atypical cases. Occasionally, it’s noted during the first year of life when associated with generalized hemihypertrophy.

**Dr. Listernick:** What’s a significant length discrepancy?

**Dr. Grayhack:** Although it’s not well defined in children, for average height adults, it’s greater than 2 cm to 2.5 cm. With this discrepancy in length, there’s probably an increased risk of back pain or hip pain or complaints. However, there are no hard data that this will lead to arthritis or permanent disability.

**Dr. Listernick:** Can you interpret the physical exam for us?

**Dr. Grayhack:** The hip exam was described because one of the more common causes of thigh pain at any age is pathology localized to the hip. She has good hip rotation. Leg lengths are measured from the anterior superior iliac spine to the medial malleolus, making sure the leg is straight.

**Dr. Listernick:** If you had seen her at a much younger age when she still had significant growth potential, what would you have done?

**Dr. Grayhack:** First, I would have told her that I don’t think that a difference of less than 2 cm at maturity would be significant. Next, we have charts that predict final limb length discrepancy based on chronologic and bone ages. Based on her age and these predictions, we would have followed her closely over time. Most children who have limb length discrepancies of less than 2 cm are asymptomatic and prefer not to wear lifts. If they start to develop an ankle contracture, a lift can be prescribed, although they often won’t wear them.

**Dr. Listernick:** How do you approach children with greater leg length discrepancies?

**Dr. Grayhack:** There are various options. Obviously, the child could use a lift indefinitely if the discrepancy is marginal. Making the shorter side longer is a very demanding treatment. Therefore, we generally shorten the longer leg by closing the growth plates around the knee (epiphysiodesis) at the appropriate time.
time. We have charts that allow us to accurately predict this time using bone age and pubertal status.

**Dr. Listernick:** So I initially told a bit of a fib. This girl was actually being followed for hemihypertrophy. Does that change your approach?

**Dr. Grayhack:** The literature doesn’t clearly distinguish whether hemihypertrophy refers to increased length of a limb or increased tissue thickness, ie, circumference. Increased thigh or calf circumference wouldn’t alter my approach to treatment of the leg length discrepancy, but it certainly does to the patient’s overall health care.

**Joel Charrow, MD, geneticist:** As John stated, I’m not aware of any formal definition of hemihypertrophy. It’s more au courant to refer to this condition as hemihyperplasia because it is presumed to be due to an increased number of cells rather than an enlargement of cells.

We tend to divide children who have hemihyperplasia into two categories: those who have idiopathic hemihyperplasia and those who have an underlying cause such as Beckwith-Wiedemann syndrome, Klippel-Trenaunay-Weber syndrome, Russell-Silver syndrome, or neurofibromatosis type 1. The risk in all these children is clearly the development of an intra-abdominal malignancy.

**Elaine Morgan, MD, pediatric oncologist:** I agree that the correct definition is not clear, but many of the kids whom we’ve seen with malignancies have “hypertrophy” limited to one unilateral small area such as the face, chest wall or foot. The commonly associated malignancies are Wilms’ tumor, hepatoblastoma, and adrenocortical carcinoma.

**Dr. Listernick:** How do you decide if the hemihyperplasia is “idiopathic” or secondary to an underlying condition?

**Dr. Charrow:** Mainly, one looks for other manifestations of an underlying disease. For example, in Beckwith-Wiedemann syndrome, you would look for an omphalocele, macroglossia, or abnormal earlobe creases. Children with Russell-Silver syndrome obviously have short stature, as well as triangular-shaped facies and clinodactyly.

**Dr. Listernick:** What are the genetics of Beckwith-Wiedemann syndrome?

**Dr. Charrow:** They’re quite complicated. Beckwith-Wiedemann syndrome is due to abnormal regulation of gene transcription in an imprinted domain on chromosome 11p15.5. There are two imprinting centers within this region, each associated with a number of different genes. Beckwith-Wiedemann syndrome may result from loss of methylation of one region on the maternal chromosome, gain of regulation of the other region on the maternal chromosome, mutation of the maternal allele of a specific gene (CDKN1C), paternal uniparental disomy of this region (both of the critical regions derived from the father), or a translocation, duplication or inversion of the chromosome at this region.

As I said, it’s complicated. Approximately half of the cases are due to the first mechanism, loss of methylation in the critical region.

**Dr. Listernick:** If a child has seemingly isolated hemihyperplasia without other manifestations of Beckwith-Wiedemann syndrome, would you consider doing genetic testing?

**Dr. Charrow:** I’m not aware of any data that would answer this question. There are probably some geneticists who would recommend the testing; many wouldn’t.

**Dr. Listernick:** Given the risk of intra-abdominal malignancies, how should we follow these children?

**Dr. Charrow:** There are some differences of opinion about the frequency of screening abdominal ultrason sound examinations. Approximately 90% to 95%
of Wilms’ tumors in these children are diagnosed before age 7 years and hepatoblastoma is almost always diagnosed before 4 years of age. Most people agree on performing ultrasonography every 3 months at least until the age of 7 years. There’s disagreement about performing them after age 7 years, although, clearly, 5% to 10% of Wilms’ tumors present in older children. In addition, we recommend serum alpha-fetoprotein measurements during the first 4 years to screen for the development of hepatoblastoma.

Dr. Listernick: Are there any data that suggest this approach detects tumors early and saves lives?

Dr. Charrow: There are a lot of anecdotal data. However, I’m aware of one retrospective study that looked at outcome in patients with Beckwith-Wiedemann syndrome. They reported that in children who had been screened, there were no cases of Wilms’ tumor that presented beyond stage II, whereas in patients who were not screened, approximately 40% had advanced stage Wilms’ tumor at the time of diagnosis.

Dr. Listernick: Do we understand the pathophysiology of this predilection for the development of tumors?

Elizabeth Perlman, MD, pediatric pathologist: Within the critical region, there’s at least one growth promoter gene, IGF2, which may affect tumor development.

Dr. Listernick: Moving forward, she was followed by serial ultrasonography for most of the first decade of life. At 16 and a half years of age, she developed sharp left-sided abdominal pain without vomiting or diarrhea. I believe that the family had long forgotten her risk of malignancy. However, ultrasonography revealed a right intrarenal mass.

Mariam Kappil, MD, pediatric radiologist: There was no prior imaging available when she presented on this admission. As discussed, usually the first study performed in children with suspected Wilms’ tumor is abdominal ultrasonography. Besides identification of the intrinsic renal mass, we are careful to try to identify tumor extension into the renal vein and inferior vena cava, common findings in Wilms’ tumor that may alter the surgical approach. In our patient, the inferior vena cava was being compressed by the mass, but we couldn’t see any definite tumor invasion.

Dr. Listernick: I remember seeing a child with unrecognized hemihyperplasia whose Wilms’ tumor extended up the inferior vena cava, into the right atrium and across into the left atrium through a patent foramen ovale.

Dr. Kappil: On the computerized tomography scan, we can see a rim of kidney around the mass that is clearly arising from the kidney. The main differential diagnosis would be neuroblastoma, which is usually easy to distinguish from Wilms’ tumor. Wilms’ tumor tends to displace adjacent structures and blood vessels, whereas neuroblastoma will often encase the vessels and grows across the midline. Calcifications are commonly seen in neuroblastoma.

Marleta Reynolds, MD, pediatric surgeon: Another aspect of imaging is that CT scans are tremendously helpful at detecting smaller lesions in the contralateral kidney. In the past, we would explore the contralateral kidney at the time of nephrectomy to confirm the absence of lesions in that kidney. In general, we perform a radical nephrectomy. However, if the tumor is unresectable, bilateral, or extending up the vena cava into the heart, we recommend preoperative chemotherapy.

Dr. Listernick: Can we see the pathology?

Agatha Bogard, MD, pediatric pathologist: She had a right radical nephrectomy in 2005. The tumor was 13.5 cm in greatest dimension. There was neither capsular penetration nor renal sinus involvement. The surgical margins were negative for tumor. The histology was blastema predominant, which is a favorable histology.

Dr. Listernick: Should our therapeutic approach to this child’s Wilms’ tumor be different because of the presence of hemihyperplasia?

Dr. Perlman: First, let me comment on the radiographic screening approach to hemihyperplasia. In general, we’re not looking for large tumors such as this girl had but rather small nephrogenic rests, which are precursors to Wilms’ tumor. Usually patients with hemihyperplasia have perihilar nephrogenic rests, which are small spherical nodules underneath the capsule of the kidney. They may grow quite large, only to subsequently regress and completely disappear. We wouldn’t want to treat these lesions with unnecessary chemotherapy. The most difficult part of the clinical management of these patients is what to do with these small lesions that are found on screening ultrasonography.

Dr. Listernick: What about these patients’ prognoses?

Dr. Perlman: That’s an even more difficult question. We have tried to develop a rational protocol for patients who have bilateral tumors and for those with tumor predisposition syndromes. Previously, they had all been grouped into one protocol. Overall, these patients had worse...
Key Learning Points

1. Leg length discrepancy may lead to thigh or hip pain.
2. For significant leg length discrepancies (>2.5 cm), treatment generally entails shortening the longer leg by closing the growth plates around the knee (epiphysiodasis) at an appropriate time based on bone age and pubertal status.
3. Hemihypertrophy, now generally called hemihyperplasia, may be idiopathic or due to underlying causes such as Beckwith-Wiedemann syndrome, Klippel-Trenaunay-Weber syndrome, Russell-Silver syndrome, or neurofibromatosis type 1.
4. Individuals with hemihyperplasia are at risk for the development of intra-abdominal malignancies, most commonly Wilms’ tumor, hepatoblastoma, and adrenocortical carcinoma.
5. Screening recommendations for children with hemihyperplasia include serial abdominal ultrasonography every 3 months for the first 7 years of life, as well as serum alpha-fetoprotein measurements during the first 4 years. Recommendations as to how to follow these children after 7 years of age are controversial.

long-term survival. However, it’s felt that these differences might not be due to differences in tumor biology but, perhaps, to overaggressive treatment of these individuals. The rationale for the current protocol is to decrease treatment of these children so they don’t develop renal failure and all its complications.

Dr. Listerick: Is older patient age at diagnosis a risk factor for worse prognosis?

Dr. Perlman: Stage for stage, tumors in older patients behave similarly to those in younger children.

Dr. Listerick: She underwent surgery and two-drug chemotherapy for 6 months, which was standard for stage II disease in 2005. Unfortunately, yearly ultrasonography at 23 years of age revealed a 7-cm mass in the renal fossa displacing the inferior vena cava and three liver masses.

Dr. Morgan: Traditionally, we stop doing ultrasonography after 5 years post-treatment. Her ultrasound was performed because we have no idea now how to factor in hemihyperplasia if the first tumor is detected at age 16 years. Being stage II at original diagnosis, we had quoted a 90% disease-free survival, although I was a bit nervous, given her advanced age at presentation. She’s now stage IV with metastatic disease. There are very few data on how to proceed. The decision was made to try to get her into remission and proceed to autologous stem cell transplantation.

Dr. Listerick: Are we offering the possibility of ovarian cryopreservation?

Dr. Reynolds: The key is time. If a child needs to receive chemotherapy or radiation immediately, we only can offer ovarian cryopreservation. Candidates for ovarian preservation undergo a laparoscopic oophorectomy and the ovary is frozen for future reimplantation or egg retrieval. In one young girl, we were encouraged to find viable follicles, which hopefully could be used in the future.

Dr. Listerick: Thanks, everybody.