

## SUBSPECIALIST CONSULT

## The Child With a Limp

*You suspect that a patient you see has a limp that may indicate a more serious condition. What is the best strategy to evaluate this child? How do you know when to treat and when to refer the patient to a specialist? And finally, which tests are most useful and which others are likely to add little to the clinical assessment, except additional cost?*

The etiology of a child's limp can range from simple and benign to a serious condition. When such a patient presents, focus on the child's history and physical examination. A good history, for example, can help to narrow down the long list of differential diagnoses and potential etiologies.

It is important to take parents' concerns seriously. There are essential questions to ask parents and patients. For example, is there pain? Is the child sick? Who noticed the limp first? Was the onset gradual or sudden? How long has the child had a limp? Is the limp getting better or worse, or is it staying the same?

When performing the physical examination, have the child walk a long distance, not just within the confines of the exam

room. Watch the child walk and/or run from different viewpoints, including the front, back, and side. Also, have the child undress so lower extremities are exposed.

During the examination, try to determine the type of limp. Common forms include antalgic (painful), Trendelenburg (associated with weakness), and limps associated with a short limb, spasticity and/or stiffness, or poor balance. Another tip is to observe the child after you ask him or her to pick up an object off the floor. If the child keeps the spine stiff, it may indicate a spinal etiology for the limp.

Try to find the point of maximal tenderness during a tabletop examination. Flex each joint through its full range. During this part of the exam, also look for any atrophy, rashes, swelling, or discoloration. Consider whether the problem can be localized. Also, remember that knee pain is hip pain until proven otherwise! Keep in mind that slipped capital femoral epiphysis can present as knee pain, so check hip internal rotation. Do not forget to do the Gowers' test in boys (have the child stand from a sitting position on the floor) because if there is

muscle weakness, it may be associated with Duchenne's muscular dystrophy, which occurs primarily in boys.

Limps generally can be divided into three age categories to help narrow the list of possible etiologies. For example, fractures and infection are common causes in children less than 4 years old. Infection becomes less common, and acute and/or overuse injuries and hip disorders (for example, Perthes disease, transient synovitis) become more common, in children between 4 years and 10 years old. Overuse and acute injuries are especially common among children older than 10 years.

Some tests are more useful than others in the child with a limp. For example, plain radiographs of the affected limb—including one joint above and below—can be useful. Ultrasound of the hip also can help if there is concern about the possibility of a septic hip; this imaging helps to detect the presence of an effusion. In a child with an acute, nontraumatic limp, laboratory assays including complete blood count with differential, erythrocyte sedimentation rate, and C-reactive protein test are recommended prior to referral.

In contrast, MRIs and bone scans should be ordered by the specialist who is going to treat the child based on the findings.

If the diagnosis is unclear after the ini-

tial examination, reevaluate the child on a weekly basis until the problem resolves or the diagnosis is established.

In general, pediatricians can observe a child whose limp is improving. Also, observe a limping child who can still play and perform all activities of daily living without interference. In addition, bilateral symptoms suggest a benign condition. Remember, idiopathic toe walking should be bilateral. Reassure parents that growing pains will not make a child limp.

Refer the child to a specialist when the limp does not improve over time. In addition, consider referral if the patient has constitutional symptoms associated with a new-onset, nontraumatic limp.

A child with a painful limp generally will need further evaluation unless there is an obvious cause. Remember that a limp associated with constant pain, even while the child is at rest and/or at nighttime, is worrisome, and a specialist may be able to help with diagnosis and management. And always be concerned about the child who loses the ability to walk. Also, don't forget to consider child abuse in the infant or toddler with multiple injuries. ■

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BY CHRISTOPHER IOBST, M.D.

## GENOMIC MEDICINE

## Old Drugs, New Tricks

As a former gene therapy researcher, I must confess that to me, nearly all attempts at gene therapy for genetic disorders have been disappointing. The sad fact is that our immune system is its own worst enemy as far as gene therapy goes, clearing attempts to use vectors to introduce new genetic material into cells and organs without breaking a sweat.

When I was a grad student, I was fond of saying (probably not originally) that with gene therapy, we were attempting to treat disorders we didn't understand, in systems we didn't understand, using gene vectors we didn't understand. At that time, many expected that, like a medical "Hail Mary," something good would come out of the considerable efforts directed at gene replacement-based therapies.

Moving forward, the prospects for successful primary gene therapy for most disorders remain distant. However, remarkable gains—fueled by discoveries in genomics—have been made in understanding the pathophysiology of many genetic disorders, and they are yielding therapeutic breakthroughs.

A particularly compelling story is the evolution of our understanding of Marfan syndrome (MFS), one of the classic autosomal dominantly inherited disorders characterized by tall stature, disproportionately long limbs, dislocated lenses, and other connective tissue abnormalities. The most devastating consequence of MFS is a predisposition to aortic root dilatation and aneurysm formation that all too often leads to death in early adulthood. Unfortunately, the disorder is not that rare, affecting about 1/5,000 individuals (as a benchmark, cystic fibrosis affects about 1/2,500 white people). It is caused by mutations in the *Fbn-1* gene, which encodes

the protein fibrillin-1, a constituent of the extracellular matrix in connective tissues and blood vessel walls.

Until recently, most investigators thought that MFS was a nearly hopeless case for targeted therapeutic interventions, largely because the defect was in a structural protein, rather than in an enzyme. In general, it is relatively easy to devise rational ways to treat disorders with enzyme replacement, but it is much harder to conceptualize treating a disorder if the cause is a structural element defect. MFS patients were therefore relegated to risky surgical correction of developing vascular abnormalities, or marginally beneficial use of beta-blockers to slow blood vessel dilatation.

However, investigators were not satisfied that a classic structural protein defect could explain all of the features of MFS, and a few years ago, they made a vital discovery: Defects in fibrillin-1 cause dysregulation of transforming growth factor-beta (TGF-beta) signaling in affected tissues.

By using mouse models for MFS and TGF-beta-neutralizing antibodies, researchers were able to show rescue of the blood vessel abnormalities. This alone would be a remarkable scientific finding, but delivering antibodies over a long period to patients isn't a much more appealing clinical solution than the prospects of gene therapy.

Then something bordering on magical happened. One group of investigators recognized that an already commonly used antihypertensive in the class of drugs known as angiotensin II type 1 receptor blockers (ARBs) also interfered with TGF-beta signaling, so they tried the drug in the mouse Marfan model.

The results were nothing short of spectacular: The vascular consequences of MFS could be prevented in

the mouse model system (Science 2006;312:117-21).

This success, coupled with the grave prognosis for MFS and the known safety profile of the ARB drugs, has led to a large prospective human clinical trial funded by the National Heart, Lung, and Blood Institute. The trial, comparing the effectiveness of losartan and atenolol in a pediatric to young adult population (aged 6 months to 25 years), will have as its primary outcome measurement of body surface-adjusted aortic root dilatation, with measurement at 2, 12, 24, and 36 months. The preliminary results are due out soon, and many in the field expect that the trial will show clear, major benefits from the use of ARBs.

It is interesting, and probably prophetic, that MFS treatment might soon be revolutionized through a careful tweaking of a formerly unrecognized but important pathway rather than through brute-force correction of the underlying genetic defect.

Expect that this will be the model for other truculent genetic disorders, not the least of which appears to be cystic fibrosis, for which a drug targeting patients with a particular genetic variant (unfortunately not the most common) has shown promising results in phase II trials in recent months.

Although almost 12 years have passed since I was a grad student, gene therapy remains the genomic medicine equivalent of a Hail Mary—a play not to be counted on or out. The difference today is that the ground game is fundamentally sound: Those 4-yard gains might carry the contest for a variety of disorders. ■

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