questons and answers

from medical presentations at the June 25, 2010, LDSF conference in Baltimore, MD

Loeys·Dietz Syndrome Foundation℠

www.loeysdietz.org

genetics

Dr. Hal Dietz
Victor A. McKusick Professor of Institute of Genetic Medicine and Professor of Pediatrics; Investigator of Howard Hughes Medical Institute

Q. According to recent findings by Dr. Dietz with the Loeys-Dietz mice models, the aortic enlargement in wild-type mice is significantly higher than the growth for Losartan-treated mice. Is that a concern?

A. The concern would be whether the treatment is causing the aorta to become too small. The answer is "no." Losartan or other medications don't take a normal sized aorta and make them smaller; they only slow down the growth of the segment of the aorta that's too big to begin with.

Q. If you're on Losartan and also a betablocker, can the betablocker interfere with the affects of the Losartan?

A. No. The combination of Losartan and a betablocker is a very good combination. We don't have evidence to suggest that the betablocker is absolutely required for the protection, but we have clear evidence that the betablockers don't do any harm—they don't block the effects of the Losartan.

Q. What's the current recommended dose for Losartan?

A. Current recommendation is 1.4 mg/kg (of bodyweight) per day. This is a minimum target dose, but there's room to go higher if needed.

Q. How do I know if I need to change my dose of Losartan?

A. It depends on the imaging studies of the aorta and other blood vessels. If everything is nice and stable, a dose of 1.4mg/kg is recommended. But if there's a creep in the size of the segment of the aorta or another blood vessel, then the dose could be increased to as high as 2mg/kg. (Losartan was the first drug in that class released by the pharmaceutical company Merck. Some of the newer generations of this drug allow more aggressive dosing).

Q. When we were first diagnosed, the protocol was that we needed scans every 6 months. Now that recommendation is every 18 months. Why the change in protocol?

A. The protocol for imaging for patients with Loeys-Dietz has changed for two reasons. First, doctors have learned over the past years that aneurysms tend to develop slowly, something they didn't know when they first recognized Loeys-Dietz just five years ago. And second, there's also the concern about radiation exposure, especially over a lifetime. Though newer CT technology has substantially lower radiation (Hopkins is one of only 3 hospitals with "flash" CT scanner which uses 1/10 the radiation of a normal scanner), our bodies can only take so much radiation. That being said, patients with a rapidly expanding aorta should have images taken more frequently.

Q. Should we still do echos annually, even if we've already done the aortic root repair?

A. Absolutely, an echo is a no-risk procedure that provides information on heart muscles and valve functions that CT scans or MRI scans show less well. So a yearly echo, at a minimum, is the right thing to do.

Q. Most of the research findings so far on Loeys-Dietz seem to focus on the effects of Losartan on the heart. What do we know about the effects of Losartan on other parts of the body?

A. This remains a largely open question, but there are two promising signs: Losartan has broader effects on Marfan's patients, and emerging data suggests Losartan is having an effect elsewhere with Loeys-Dietz patients too.

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Q. Are there any problems for the future of kids with Loeys-Dietz, particularly with pregnancy?

A. LDS is what's called a dominant condition, meaning you only need to have one abnormal copy of one of these genes to have the condition. This means that people with LDS have 50-50 chance of passing on LDS to their offspring.

There are a few ways to manage that issue. A prenatal diagnosis, where a small amount of fluid is taken from the uterus, can show whether there's a mutation of the gene. An alternative is something called pre-implantation diagnosis which involves getting the eggs from the mother, sperms of the father, and fertilizing outside the womb until there's an 8-cell structure. At that point a single cell is taken from those 8-cell embryos. The embryos that don't have the mutation can then be implanted back in the uterus. This could potentially be a way for a person to decide whether to have a child without the need for terminating an established pregnancy.

We do know there are risks to a woman with LDS who becomes pregnant, including blood vessel enlargement or rupture, and uterine rupture. That risk extends even 3-4 weeks after a child is delivered. If a woman with Loeys-Dietz decides to become pregnant, she should be followed by a high-risk OB.

Many women with Loeys-Dietz have decided to have the aortic repair done before pregnancy even if they're not yet at risk. Most people with LDS can have a procedure called a valve-sparing repair. In that procedure you get to keep your natural aortic valve and don't need blood thinners, which would make pregnancy much more difficult.

We need to learn more about the implications of LDS for pregnancy before knowing precise answers. Bottom line is that a lot of women have had successful pregnancies, but it does require a lot of planning and forethought and the risks would vary from person to person depending on their circumstances.

Q. Any correlation between LDS and eye problems?

A. There are some eye issues with people with Loeys-Dietz. As a group there's no lens dislocation, or the severity of near sightedness that we see in Marfan's. What we do see is a low risk of near sightedness and a mild risk of retinal detachment.

Q. Why don't doctors at teaching hospitals know about Loeys-Dietz?

A. With thousands of diseases that are vying for attention of medical schools and students, issues that are less frequent, like Loeys-Dietz, get less attention. The word on Loeys-Dietz is getting out though, largely as a result of medical presentations by Dr. Dietz and other doctors at Hopkins. Education is also a major mission of the Loeys-Dietz Syndrome Foundation. The right answer is that people with Loeys-Dietz or their parents are their own best advocates.

Q. What are the findings of heart transplants among Loeys-Dietz patients?

A. One percent of patients with Marfan's have heart muscle problems that are yet to be explained. Those same studies are planned with LDS mice. The focus of these studies in LDS will initially remain on aneurysms, then will consider other heart problems.

cardiacsurgery

Dr. Duke Cameron
Cardiac Surgeon in Charge, the James T. Dresher Sr. Professor of Surgery, Director of Pediatric Cardiac Surgery, Johns Hopkins Hospital

Q. Is there a size limit by which one should decide to close an atrial septal defect (ASD)?

A. No, there's no one specific size since what matters is the flow of blood going through the ASD. Larger ones the size of a quarter with lots of blood going through are no-brainers, and pin-size ones are inconsequential. For all those in between, it really depends on how much blood is leaking, which can be estimated with echos, catscans, and MRIs. Rule of thumb: if the amount of blood going through the right side of the heart is more than 1.5 what's going to the left side of the heart, it should probably be closed. The normal ration is 1:1.

Q. With pig valve, does it have to be replaced in 5 years?

A. No, depends on the patient. If you were 2 years old, it'll probably wear out in 5 years, but there's so much variability.

Q. Concern with dilated pulmonary valve?

A. LDS patients tend to have dilated pulmonary valves. These dilations seems to progress over time, but a rupture has never been documented. A major difference is that the pressure at the pulmonary root is four times less than at the aortic root.

Q. Should LDS teens be managed like LDS adults or kids with respect to when to intervene?

A. LDS patients between the ages of 12 and 18 behave just like adults, so should therefore be managed according to adult guidelines.

Q. What's the z-score and why does it matter in determining when to intervene?

A. The Z-score is a statistical measure that just tells you how far from the average you are—it says nothing about the level of risk you're facing of rupturing the aorta. What matters in deciding when to operate is the absolute size of the aorta.

The question of whether we need to index the size of the aorta to the patient's size remains unsettled among doctors, yet an aneurysm is a balloon, regardless whether it's sitting inside a small person or a larger person. It's like blowing up a balloon inside a car—whether it ruptures doesn't matter how big the car is. It's the size of the balloon and the pressure that matter.

Q. Is a 3cm diameter of the aortic root aneurysm the right time to intervene?

A. Yes, and that's been the protocol for about 3 years.

Q. My daughter had her procedure done in 2005. How long will it last?

A. Theoretically, the valve-sparing procedure can last a life time. In practice, we don't know for sure because this procedure has only been around for 15 years. There are some concerns that having these flaps constricted in a plastic tube may weaken them over time. But if this procedure is getting kids through childhood and early adulthood without mechanical valves, it's still a better option. And the wear and tear of valves can safely be monitored through echos.

Q. If you've already had a dissection involving the aorta, are there data that tell us what to expect in the future?

A. Not for LDS, but we do have data for people without LDS or with Marfans. If LDS patients turn out to be like these others, then we can expect at least 1/3 of them needing more than just the aortic root replaced.

allergies and gastroenterology

Dr. Pamela Guerrerio
Assistant Professor,
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Dr. Anthony Guerrerio
Pediatric Gastroenterologist and
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Q. Is Pediasure good for children with LDS?

A. In the absence of any food allergies, Pediasure is a fine nutritional supplement.

Q. Are there wide food groups to avoid?

A. What to avoid is very specific to individuals. A history of how a child or individual reacts to each food is important in how we interpret tests.

Q. How long do you have to take a food out of the diet before you know if that's contributing to the problem your child may be having?

A. Depends on the type of allergy. If it's of the type that you have an immediate reaction when exposed to a particular food, that's a clear one. The more tricky one is when there's intestinal inflammation. In that case, there may be some improvement a week after having removed the food from the diet, but it usually takes up to 6 or even 8 weeks for inflammation in the GI track to actually go away.

It's important to note that sometimes even just a bit of exposure is enough to cause the inflammation. Milk, for instance, can be in pretzels and cookies, and lactose is present in all sorts of things, even some medications. It's very important to read all labels when trying to figure out what the patient is allergic to.

Q. Is there a different treatment strategy for people with LDS with allergies?

A. No, allergies among people with LDS should have the same treatment as that of the general population. The one exception is asthma. Many children with LDS have asthma caused by sinus disease; once their sinus disease is treated, their asthma improves. So we're very aggressive about treating sinus disease if they're also having asthma problems.

Q. Does food allergy develop over time or are people born with it?

A. Both. Most of the allergies with acute reactions typically develop very early, by the age of two. The other type with inflammation in the GI tract could develop later, even as teenagers or adults.

Q. Can an inflammation of the esophagus cause Barrett's esophagus?

A. No, they're very different types of inflammation. Eosinophilic esophagitis can be painful and can cause poor growth, vomiting, and diarrhea, but does not seem to predispose people to cancer or pre-malignant pre-cancer.

Q. Is there a change in the shape of the eosinhophils?

A. No, they don't appear to look any different. Patients with LDS may have more eospinhophils, but these eospinhophils don't appear to do anything differently.

Q. What percentage of LDS patients have food allergies?

A. In a survey of 58 people with LDS, 22 percent had food allergies. But that's probably an underestimate because the study used a very stringent definition of food allergies (only those patients for whom there were lab and scope reports). The same survey found that 15 percent had eosinophilic esophagitis (again, probably a gross underestimate). The prevalence is believed to be much higher because almost every mouse with the LDS mutation has eosinophilic esophagitis.

Q. With blood test for food allergies, what do you test for and is it the same for everyone?

A. There's a long list of foods commonly associated with allergies and eosinophilic esophagitis. Doctors evaluate these results, but always in light of what parents/patients have to report.

Q. What's the preferred test to assess food allergies—skin test or blood test?

A. Blood tests are generally preferred because they actually provide a number—so not just whether the person has an allergy or not, but also the strength of the allergic reaction.

orthopedic surgery

Dr. Paul Sponseller
Chief of Pediatric Orthopedics; Professor in Orthopedic Surgery, Johns Hopkins University

Q. From an orthopedics perspective, what should be the precautions for people with Loeys-Dietz later in life?

A. We don't know enough to rule out any one particular activity in general. People with LDS may experience more fatigue and pain, but are under no additional risks for normal activities. Patients should be guided by their own experiences. If cervical instability has been identified, they should discuss limitations with the treating orthopaedist.

Q. What can parents do to help manage their kids' scoliosis?

A. Sometimes it's just a matter of watching and waiting. Bracing probably helps some of the milder curves, but not with more severe curves. Surgical intervention is generally reserved for more severe curves, when the curvature is more than 60-70 degrees and can affect the heart and lungs.

Q. How to manage kids with decreased bone density?

A. There's no data on the overall incidence of osteopenia and osteoporosis, but clearly they exist. Parents can monitor with X-rays and, if needed, a DEXA scan. The only real treatment for osteoporosis is having an appropriate level of activity within the range of the patient's abilities and ensuring a more than average intake of calcium and vitamin C (caution with medications that can inhibit the absorption of calcium/vitamin C).

Q. Besides water exercises, what other activities are recommended for people with LDS?

A. For weight bearing and muscle strengthening, it really depends on the individual, their preferences and abilities. Swimming is good for many reasons but isn't ideal for weight bearing because weight is actually relieved by water. A physical therapist can be an option to help advise possible activities.

vascular surgery

Dr. James Black
The Bertram M. Bernheim, MD Associate Professor of Surgery, Johns Hopkins University

Q. What are the implications of arterial tortuosity?

A. There is no evidence to suggest that arterial tortuosity in and of itself will put patients at risk for dissection in the carotid artery. This is important to keep in mind, especially since doctors not familiar with LDS may think otherwise.

Q. If a patient has imaging studies done outside of Hopkins, can doctors at Hopkins still use them in their assessment?

A. Yes, absolutely. Doctors at Hopkins trying to reduce patient exposure to radiation as much as possible. When scans are sent to Dr. Dietz, they are generally shared with Dr. Black and lots of others at Hopkins.

Q. My 8-yr old had a brain MRA showing mild dural ectasia. He also has carotid tortuosity. Are these things linked? Have you seen this in other patients?

A. Yes, tortuosity can occur in the brain. Usually it's not the tortuous blood vessel itself that develops an aneurysm; it's where the blood vessel comes up from the base of the neck and splits into what we call the middle cerebral artery and the anterior cerebral artery. The good news about aneurysms in the brain is that many of them can be repaired with coiling, which is a minimally invasive way to repair. Also, aneurysms have been observed, but not dissections.

Q. I had an early dissection. Is there a point where pressure gets worse when you get away from the higher vessels?

A. As consequence of aging, most blood vessels lose some of the elasticity that we have in childhood and teen years. The elastin we have is essentially given to us at birth. Using medications to maintain these elastin fibers is key to keeping them working well for a lifetime.

When someone has a dissection, it's essentially a longitudinal cut along the aorta's many layers. So if someone suffers an early dissection and nearly the entire circumference of the aorta is dissected, then there's damage to the entire wall of the aorta. Losartan won't necessarily improve the situation because the damage is done.

Q. What are the long-term care concerns with an elephant trunk procedure?

A. This procedure is done when someone undergoes replacement of the aortic arch and it's thought that the descending aorta is going to be at risk for developing an aneurysm. This technique means that they leave a piece of graft dangling inside to be accessed much easier for eventual replacement of the aorta running through the chest. Some people are concerned about developing clots, but likelihood is very low and doesn't justify the use of blood thinners.

Q. Earlier studies showed a strong correlation between the severity of Loeys-Dietz craniofacial characteristics and the aggressiveness of the aortic aneurysm. Does the same correlation hold for aneurysms elsewhere in the body?

A. No. Most of the original correlation cited in the 2005 article was with the ascending aorta.

Q. What are the long term implications of a carotid dissection, especially with respect to chronic headaches?

A. Carotid dissections can occur in patients with and without connective issue disorders. Generally the onset of a carotid dissection is treated with a short dose of anticoagulation, continued for 6 months. People tend to have headaches associated with nerves in the back of the head. So headaches in the back of the head are possibly related to the carotid, but wouldn't justify pathways for frontal headaches.