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## Early Surgery Recommended for Those with Life-Threatening Vascular Disorder

According to a new study of patients with a life-threatening condition known as Loeys-Dietz syndrome (LDS), children with the inherited vascular disorder should be considered early candidates for surgery to prevent lethal rupture of the aorta, the heart's main artery.

The researchers said that in some cases, the clinical symptoms of LDS can be very similar to those of another vascular disease known as vascular Ehlers-Danlos syndrome. "Distinguishing between the two diagnoses -- which can be done through gene testing -- is critical. While early surgery can prevent aortic rupture that is linked to LDS, the same surgery often leads to fatal complications in patients with vascular Ehlers-Danlos syndrome," said senior author Harry C. Dietz, a Howard Hughes Medical Institute investigator at The Johns Hopkins University School of Medicine.

The current study, published in the August 24, 2006, issue of the *New England Journal of Medicine (NEJM)*, was directed by the same researchers who first identified LDS in 2005. The research team, led by Dietz and Bart L. Loeys, who is now at the Ghent University Hospital in Belgium, has now expanded its analysis to include members of 42 additional affected families -- including many whose symptoms were less apparent than those who were studied in the original group. The study published in *NEJM* has revealed new characteristics of LDS that have important implications for diagnosis and treatment.

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In their initial studies of the first 10 families, Dietz, Loeys, and their colleagues described a new syndrome that they called LDS. People with this relatively common disorder have an increased risk that their aorta will rupture earlier in life than people with other aortic aneurysm syndromes, such as Marfan syndrome. Aneurysms in patients with LDS are also more severe and more widely distributed throughout the arterial circulation, rather than strictly at the aortic root near the heart. Other risks associated with LDS are a tendency for rupture of the bowel and rupture of the uterus during pregnancy. In the clinic, LDS can be recognized by physical features such as widely spaced eyes, cleft palate, divided uvula, and premature fusion of the skull bones.

In studying the larger group of patients described in the *NEJM* article, Dietz said the team was able to identify additional characteristics of LDS that were not apparent earlier. "We learned that the rate of life-threatening complications of pregnancy is extremely high -- about 50 percent -- among women with LDS, regardless of whether they have the characteristic craniofacial features," said Dietz. "We also learned about new manifestations of LDS, including cervical spine instability that can lead to spinal cord injury if not surgically corrected; osteoporosis with a tendency for bone fractures, abnormal development of the teeth; and occasional primary learning disability not caused by evident structural brain abnormalities," he said.

In earlier studies, the researchers traced the cause of LDS to mutations in the gene that produces the receptor for a protein known as transforming growth factor-beta (TGF $\beta$ ). TGF $\beta$  is a chemical messenger that influences the growth and other physiological functions of cells. Receptors are proteins embedded in the membranes of cells, which activate cell responses when a chemical messenger such as TGF $\beta$  plugs into them. There are two types of TGF $\beta$  receptors (1 and 2), either of which can be mutated in LDS, said Dietz.

"In the first ten patients, we recognized that this was an extremely aggressive disease," said Dietz. "It's one in which vessels tend to rupture at small sizes, at young ages, and throughout the body. In those initial patients, we focused on the most severely affected people, because they were the ones whom we recognized first. But in order to understand the diagnosis and treatment implications for the whole spectrum of patients with this condition, we needed to analyze a broader patient population. We didn't know how common the disease was, but since the initial publication we have continued to identify many new families with the disorder."

In the new *NEJM* study, the researchers analyzed the pathology and genetic basis of LDS in 52 affected families. These families included those exhibiting more subtle abnormalities of the uvula or the face and skull that are characteristic of the disease.

The researchers also included patients originally diagnosed with a disease called vascular Ehlers-Danlos syndrome, but who lacked the characteristic gene mutation associated with that disease. The symptoms of vascular

Ehlers-Danlos syndrome overlap those of LDS.

"When we genotyped these patients, we found that many did, indeed, have mutations in the gene for a TGF-beta receptor," said Dietz. "These people did not have the craniofacial features typical of LDS, so this told us that mutations in the same receptor gene can lead to characteristics that might be mistaken for vascular Ehlers-Danlos syndrome."

Genetic analyses of the 52 LDS families showed that all affected family members studied had mutations in one of the TGFβ receptor genes, said Dietz. Importantly, he said, all of these patients had clinical features that would exclude Marfan syndrome or familial thoracic aortic aneurysm. Furthermore, people with those disorders have not shown mutations in TGFβ receptor genes in our experience. Dietz said. He noted that the new study shows that LDS patients can be clinically distinguished from those with the other disorders.

"Another major objective of this study was to ask whether a broader analysis of people with LDS could help improve management principles for the disorder," said Dietz. "And the answer was 'yes.'" They found that mutations in the TGFβ receptor genes were associated with very aggressive progression of the disease - more severe than that seen in patients with Marfan or vascular Ehlers-Danlos syndrome, Dietz said. Patients with LDS survived only to an average age of 26.

The team also found that surgery to prevent aortic rupture was very successful in patients with LDS, and could be done early in life, even in infancy. "That surgery should be performed at aortic dimensions much smaller than those at which one would operate on for Marfan syndrome," Dietz said.

It is important for clinicians to distinguish between LDS patients and those with vascular Ehlers-Danlos syndrome, because while the former patients do well in surgery, the latter do not. "Surgeons report that trying to repair arteries in patients with vascular Ehlers-Danlos syndrome is like trying to sew together wet tissue paper; so surgery should not be done in these patients unless there's a strong conviction that the patient will otherwise die shortly," he said.

Dietz added that although the differences between the type I and type II LDS (identified by the presence or absence of craniofacial characteristics, respectively) do not make difference in management of the disease in adults, the two types lead to important distinctions in children. "Type I LDS produces earlier cardiovascular problems, and we have seen deaths due to aortic rupture as early as six months of age in these patients," he said. "So, when we see children with severe craniofacial features and the type I disease, we are moving ahead with surgery as soon as their body is big enough to accept a graft of sufficient size to accommodate growth."

The paper's findings suggest specific diagnostic and treatment steps for patients with LDS, said Dietz. "We suggest that all people with TGF-beta receptor mutations need frequent cardiovascular imaging that extends from the top of the head through the pelvis -- as opposed to the focus on the ascending thoracic aorta in people with Marfan syndrome or familial thoracic aortic aneurysm," he said. "We now know that all people with TGF-beta receptor mutations need an evaluation of the cervical spine; instability can be life-threatening but is readily fixable. Women with LDS should be counseled regarding the high risk of catastrophic complications during pregnancy. If they move ahead with pregnancy, they need to be followed by an obstetrician trained to manage high-risk pregnancies. They also need frequent cardiovascular imaging, and they need to understand the risks of rupture of the vessels and uterus, both during and immediately after pregnancy," said Dietz.

Dietz and his colleagues are now testing whether drug treatment of LDS is beneficial. Based on successful animal studies, the researchers have already begun testing whether a commonly prescribed blood pressure drug, losartan -- manufactured by Merck under the brand name Cozaar -- can prevent aneurysms in patients with Marfan syndrome. They are now beginning to use the drug in patients with LDS, he said.

Losartan acts by reducing TGF $\beta$  activity. Since the mutations associated with LDS seem to enhance TGF $\beta$  signaling, the researchers are now using a mouse model of LDS to explore the efficacy of TGF $\beta$ -blocking drugs, said Dietz.

Dietz and his Johns Hopkins colleagues collaborated on the studies with researchers at the University of Washington, Seattle; Ghent University Hospital in Belgium; University of Texas, Houston; University Hospital, Lille, France; Harvard Medical School; Ospedale Galliera, Genoa, Italy; New York University School of Medicine; University of Pennsylvania; and Washington University School of Medicine.