

## Loeys-Dietz Syndrome – an Overview

### Introduction

Loeys-Dietz Syndrome (LDS) is a dominantly inherited systemic connective tissue disorder with additional skeletal (LDS type 1) or cutaneous (LDS type 2) manifestations. LDS1 and LSD2 show clinical overlap with Marfan Syndrome (MFS) and vascular Ehlers-Danlos Syndrome (MFS), respectively. Morbidity and mortality in LDS are largely due to vascular complications from aortic aneurysms and dissections and can be reduced by surgical intervention. It is very important to distinguish LDS1 from MFS, since LDS-associated aortic aneurysms are more aggressive than those observed in patients with MFS and require surgical intervention at an earlier age and a smaller degree of aortic dilation than is recommended for MFS patients. In addition, LDS-associated aneurysms are not limited to the aortic root, but may occur throughout the arterial tree. Many of these distant arterial aneurysms cannot be detected by echocardiography, the method most commonly used for monitoring aortic dilation in MFS patients, but require screening with magnetic resonance angiography (MRA) or computed tomography (CT). Distinction of LDS2 from vascular Ehlers-Danlos Syndrome is also crucial, since prophylactic surgery is recommended only for LSD2, but not for vascular Ehlers-Danlos Syndrome, where the risk of fatal complications during vascular surgery is too high due to extreme tissue friability.

### Clinical Presentation

LDS1, which accounts for 75% of all LDS cases, shares skeletal manifestations such as arachnodactyly, pectus excavatum or pectus carinatum, scoliosis, and joint hypermobility with MFS. Distinction of LDS1 from MFS is often, but not always, possible based on the presence of characteristic craniofacial manifestations (bifid uvula or cleft palate, hypertelorism, and/or craniosynostosis) or absence of ectopia lentis. In contrast, LDS2, which is

characterized by velvety and translucent skin, easy bruising, and widened, atrophic scars, is not clinically distinguishable from vascular Ehlers-Danlos Syndrome.

### Diagnosis and Treatment

Both forms of LDS are caused by mutations in the genes *TGFBR1* (accounting for about 25% of LDS) or *TGFBR2* (accounting for about 75% of LDS), which code for the transforming-growth factor receptor 1 and 2, respectively. Therefore, genetic testing can help to diagnose LDS and to differentiate LDS from MFS and vascular Ehlers-Danlos Syndrome, which are caused by mutations in *FBN1* and *COL3A1*, respectively. Once the familial *TGFBR1* or *TGFBR2* mutation has been identified through extensive genetic testing of the index patient for a family, genetic testing for the familial mutation can be used to identify at-risk family members at an early age, allowing regular cardiac screening and timely surgical intervention as well as treatment with beta-adrenergic blockers or other medications to reduce hemodynamic stress. LDS patients might also benefit from treatment with losartan, a TGF-beta antagonist that has shown early promise in the treatment of MFS patients (4). In addition, at-risk individuals are advised to avoid all activities that increase the risk of aortic dissection even at small degrees or rates of aortic dilation, such as contact sports, high-intensity or isometric exercise, and routine use of agents such as decongestants that stimulate the cardiovascular system. Antibiotic prophylaxis for dental, gastrointestinal, or genitourinary procedures may also be advised. Carriers of LDS-associated mutations should also be aware of an increased risk of aortic dissection and/or rupture during pregnancy and delivery and other catastrophic complications of pregnancy such as uterine rupture.

Importantly, genetic testing for a known familial mutation can also identify family members who are not at a highly increased risk of LDS.

## References

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