time of 14 seconds; she has edema and is not taking a diuretic. A physician might mistakenly assume that this patient is not very sick. Yet, her risk score is 7.2, indicating that without transplantation her chances of surviving 2 years are little better than 50%, and her chances of surviving 7 years are practically nil.

Patients should be referred for transplantation when their 1-year chance of survival falls below 90%, ie, when their risk score is 6 or higher. An even simpler rule of thumb is to refer when the bilirubin level increases to 2 mg/dL or higher. Although such patients may seem well, the typical waiting time for a transplant is 1 to 2 years, by which time their risk scores will be higher.

Transplantations are ideally performed when the risk score is between 7 and 9. Patients with scores over 10 tend to have poor outcomes after transplantation.[18] Only 3,500 to 4,000 donor livers are available in the entire United States per year; therefore, at some point we as a nation will have to recognize that some patients are too sick for transplantation, and to use this scarce resource optimally, we will have to reserve transplantation for patients with lower risk scores.

Refer for a transplant at a risk score ≥ 6 bilirubin ≥ 2

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Diagnosing Marfan syndrome is still based on clinical characteristics

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ABSTRACT

Despite new genetic findings, the best way to diagnose Marfan syndrome is still the classic clinical manifestations.

PHYSICIANS WILL HAVE TO CONTINUE to rely on clinical findings—family history, tall slender habitus, ocular abnormalities, and potentially fatal cardiac abnormalities—in diagnosing Marfan syndrome, even though investigators recently identified the gene that, if defec-

tive, causes this hereditary condition. Because the mutations in this gene are so variable, a genetic test that is a reliable diagnostic tool is unlikely to be available in the near future.

In this brief overview of the features of Marfan syndrome in young adults and in adolescents, we describe the options for medical and surgical treatment and the advisability of Marfan syndrome patients exercising or becoming pregnant.

THE CAUSE: MUTATIONS IN *FBN1* GENE

The *FBN1* gene on chromosome 15 contains the code for the connective tissue protein fibrillin. A variety of mutations in this gene can cause Marfan syndrome.

Unfortunately, almost every mutation of *FBN1* that causes Marfan syndrome is different, even within the same family. In addition, some mutations of *FBN1* can cause only isolated features of Marfan syndrome, such as the ocular or skeletal manifestations, without the life-threatening cardiovascular problems. All of these factors limit the use of a direct mutational analysis as a diagnostic test.

FAMILY HISTORY USUALLY POSITIVE

Marfan syndrome is autosomal dominant, meaning on average one out of two children of parents carrying the gene will have full-blown Marfan syndrome.

However, in 15% of cases there is no family history of the syndrome, and in these cases the syndrome probably arises through spontaneous mutation of the *FBN1* gene.

For Marfan syndrome to be diagnosed, the patient must have a family history of the syndrome and in addition have manifestations in two of the three clinical systems described below (ocular, skeletal, cardiovascular). If there is no family history, then manifestations must be present in all three of the systems.

OCULAR MANIFESTATIONS

Probably the most underevaluated aspect of Marfan syndrome is its ocular manifestations. Often at the Cleveland Clinic we see patients who have been referred because of their phenotype, but who have not had their eyes examined.

Most patients with Marfan syndrome have refractive errors, most are nearsighted, some have glaucoma, and a few have presenile cataracts or retinal detachment.

However, the classic ocular finding is lens dislocation. Unlike the lens dislocation in homocystinuria, in which the lens is displaced downward and posteriorly, in Marfan syndrome the dislocation tends to be upward and anteriorly. However, even dramatic dislocations can be difficult to see during a routine ophthalmologic exam. All patients with Marfan syndrome need a detailed slip-lamp examination, preferably by someone experienced in identifying the subtle lens dislocation that characterizes this syndrome.

SKELETAL MANIFESTATIONS

Patients are usually evaluated for Marfan syndrome because of their phenotype or skeletal manifestations.

Height. Marfan patients are extremely tall and thin: men are often more than 6 feet 5 inches tall, and women are more than 6 feet tall. Often their arm span is greater than their height. However, not all persons who are unusually tall should be evaluated for Marfan syndrome. Often, height is accompanied by other skeletal characteristics listed below.

Ocular evidence of Marfan syndrome is often underevaluated

Arachnodactyly. About 90% of Marfan patients have the long, slender fingers and toes of arachnodactyly —literally, "spider fingers." In fact, this condition is so closely linked to Marfan syndrome that in the past it was used as a synonym for the condition.

Hyperextensible joints. Joint elasticity is very common in Marfan patients, and many of them take delight in demonstrating the unusual maneuvers they can perform, such as bending their wrist or thumb back unusually far, or wrapping their arms around their neck. Spontaneous dislocation of the hip, knee, or ankle is common.

Chest deformity. Many Marfan patients exhibit pectus excavatum ("funnel chest") and some exhibit pectus carinatum. Pectus excavatum is much more common.

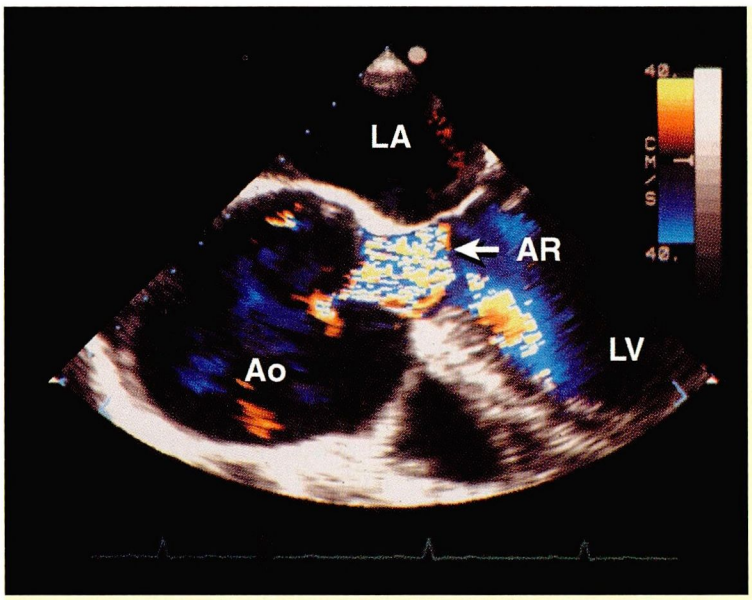

FIGURE 1 A Doppler transesophageal echocardiogram of an adult male with Marfan syndrome. Note the dilatated aorta (Ao) and the resultant aortic regurgitation (AR). LA, left atrium; LV, left ventricle.

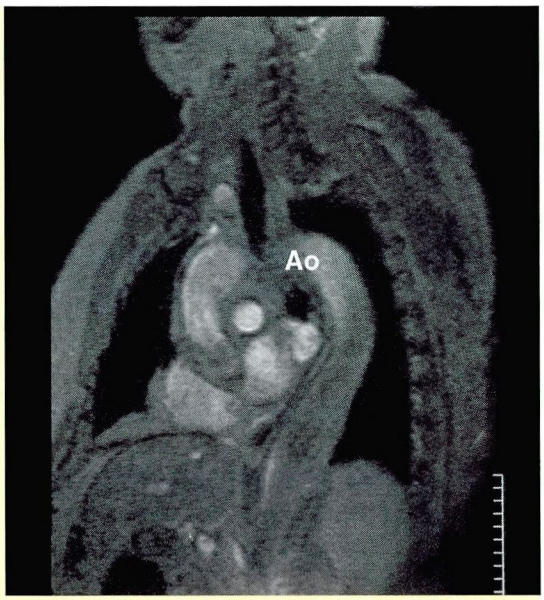

FIGURE 2 A magnetic resonance image (MRI) of the same patient, illustrating how MRI can image a larger portion of the aorta (Ao) in Marfan syndrome patients than echocardiography.

COURTESY WILLIAM J. STEWART, MD

Scoliosis often occurs in Marfan syndrome, but is usually not severe.

A high, arched palate is also common.

Thus, the classic phenotypical appearance of a Marfan patient is a combination of the above characteristics. I have found that many Marfan patients have a characteristic long, thin facial appearance, but this personal observation has not been scientifically studied.

CARDIOVASCULAR MANIFESTATIONS

Although many of the manifestations of Marfan syndrome described above are striking, the most feared manifestations are in the cardiovascular system, particularly aortic dissection leading to sudden death.

Mitral valve disease in children, aortic disease in adolescents and adults

In young children, the most common cardiovascular feature of Marfan syndrome is mitral valve disease, particularly mitral regurgitation. However, in teenagers and young adults the most common feature is aortic root dilatation, with either aortic root aneurysm, or acute or chronic aortic dissection.

The life expectancy of Marfan patients is significantly reduced. In some studies, the mean age at death of untreated patients was approximately 28 years, and most patients died of cardiovascular complications.

Diagnostic imaging techniques

Doppler echocardiography is useful both for the cardiovascular workup for a patient suspected of having Marfan syndrome, and in ongoing, follow-up evaluation of Marfan patients (FIGURE 1). Using this technique we can examine the mitral valve and measure the aorta, aortic root, and left ventricle. Its limitation is that it does not image all of the aorta perfectly, whereas Marfan syndrome can cause diffuse dilatation in the aorta.

Magnetic resonance imaging. Although we use Doppler echocardiography for early diagnosis and routine follow-up, at some point in the evaluation I recommend an examination with magnetic resonance imaging to get a very clear picture of the entire aorta (FIGURE 2).

TREATING MARFAN SYNDROME

Beta-blockers

Because beta-blockers decrease heart contractility and rate, they might conceivably slow the progression of aortic dilatation in Marfan syndrome. In fact, Shores and colleagues conducted a randomized trial in 70 patients with Marfan syndrome and found that treatment with propranolol did slow the rate of aortic dilatation, reduce the development of aortic complications, and increase the survival rate.

In my experience, the problem with beta-blocker therapy in Marfan syndrome patients is that young children and teenagers often suffer from side effects such as night terrors and sleep disruptions. Adults often fare better.

Nonetheless, because this study was small, the efficacy of treating Marfan syndrome patients with beta-blockers remains controversial. My own sense is that beta-blockers are most beneficial after surgery.

Surgery

In the 1960s and 1970s, the rate of successful surgical repair of aortic aneurysms and dissections associated with Marfan syndrome was dismal, often with a mortality rate of 50%. Today the surgical mortality rate is much lower, about 1% to 2%, and we intervene much more aggressively, using a composite graft containing an aortic valve.

In the past, we would operate on patients when their aortic diameter reached 6 cm (normal in an adult is from 3.5 cm to 4.0 cm). We now operate on patients with an aortic diameter of 5 cm or even less, if there is a strong family history of Marfan syndrome with aortic dissection and if there is dilatation of the aorta, with or without aortic incompetence and symptoms. We do not wait for symptoms or for the aortic valve to leak.

SHOULD MARFAN PATIENTS EXERCISE?

Given their unusual height and thinness, people with Marfan syndrome are often drawn to basketball and volleyball before they are diagnosed. In fact, the sudden death of Olympic volleyball champion Flo Hyman in 1986 led to increased awareness of this syndrome.

Unfortunately, there have been no good studies of exercise in Marfan patients. We do not allow them to lift weights or participate in contact sports. Also, given the documented instances of death of Marfan patients playing volleyball and basketball, we restrict these activities as well. Less strenuous exercise, such as walking, jogging, or tennis, is allowed.

IS PREGNANCY SAFE FOR MARFAN PATIENTS?

Some physicians feel that Marfan patients should not become pregnant. We have not found that to be the case, although these patients are at high risk and should deliver in a high-risk obstetrics setting. Most of our experience involves women with an aortic diameter of approximately 4 cm. Women with more severe aortic dilatation are at greater risk if pregnant.

Beta-blockers may slow the rate of aortic dilatation

SUGGESTED READING

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