COVER STORY

Cardiovascular problems in Turner syndrome are a major concern

Although not necessarily in the realm of an endocrinologist's care, problems such as aortic dissection are of high importance.

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Since Turner syndrome was first described in 1938, pediatric endocrinologists, cardiologists and other specialists have done extensive research to better understand the disorder and improve quality of life for patients. Many advancements in the treatment of the disease have been made; at present, for example, growth hormone therapy can increase final adult height in women with Turner syndrome, and assisted reproductive techniques can help women achieve pregnancy.

However, there is still work to be done to improve care for patients with Turner syndrome, and there are some known issues in the disease that are being examined. One such issue is the increased risk of certain cardiovascular problems, and although rare and perhaps outside the scope of an endocrinologist's treatment for the disease, aortic dilation, dissection and rupture remain major concerns for experts caring for girls and women with Turner syndrome.

"Endocrinologists don't necessarily have anything to do with, say, the treatment of cardiovascular problems, but they have to make sure that it gets done and that the patients get referred," **Paul Saenger, MD, MACE,** professor of pediatrics, Albert Einstein College of Medicine, told Endocrine Today. "Many of these patients with Turner syndrome see adult endocrinologists and never get an MRI done because [the endocrinologist] doesn't think about it. Then, the patient gets pregnant and they run into problems."

For this reason and others, a multidisciplinary approach to treatment of Turner syndrome would help provide the best possible care for these patients.

Cardiovascular system concerns

Along with endocrine advancements in treatment for Turner syndrome — such as GH for height and estrogen replacement therapy for pubertal development — has come an increasing realization that Turner syndrome carries higher risks of cardiovascular disease and events. The occurrence of aortic dilation, dissection or

rupture is one of the major concerns in Turner syndrome, and is associated with other risk factors including aortic valve abnormalities, aortic coarctation or dilatation, and systemic hypertension.

Paul Saenger, MD, MACE, is Professor or Pediatrics at Albert Einstein College of Medicine, N.Y.

Photo by J. Torres

Research on the frequency of aortic dissection or rupture can be found in an open-label, multicenter, postmarketing surveillance study called the National Cooperative Growth Study (NCGS). The NCGS was established in 1985 by Genentech as a means of monitoring safety and efficacy of its GH products. It is the largest database of Turner syndrome in the United States, including 5,220 individuals. **Katrina Bolar, MD,** et al examined the frequency of certain specific adverse events in the population of patients with Turner syndrome in the NCGS. The results were published in the Journal of Clinical Endocrinology and Metabolism that appeared online in November 2007.

Through June 2006, 442 adverse events were reported, including 117 serious adverse events. Events known to be related to Turner syndrome were detailed; five of the seven reported deaths in the Turner syndrome population were due to aortic dissections or ruptures. Importantly, the incidence of aortic dissection or rupture was "likely unrelated to rhGH" therapy; "it is difficult to define the role, if any, of GH therapy in the cardiac events described," the researchers wrote.

What more needs to be done to improve care for patients with Turner syndrome?

Another clue into the aortic dissection rates in Turner syndrome comes from a study by **Claus Gravholt, MD,**et al, published in 2006 in Cardiology in the Young. The researchers in this study in Denmark and Sweden found that aortic dissection occurred at a rate of about 36 per 100,000 person-years in Turner syndrome compared with six per 100,000 person-years in the general population.

Clinical practice guidelines for the care of girls and women with Turner syndrome were released online by the Turner Syndrome Consensus Study Group in the Journal of Clinical Endocrinology and Metabolism in October 2006. According to the guideline's authors, "recent studies suggest a broader spectrum of cardiovascular system abnormalities in Turner syndrome than previously recognized." The optimal care of patients with Turner syndrome includes significant attention paid to the cardiovascular system and cardiovascular defects.

Among many other points made in the guidelines, aortic dimensions should be regularly ascertained using MRI among patients with hypertension, and education of both the patient and parents should be undertaken if there is an increased risk of aortic dilatation or dissection. "Patients with a wide aortic root or aortic dilation should also

not engage in contact sports," Saenger added.

According to Saenger, the sensitivity of MRI in the detection of cardiovascular problems in patients with Turner syndrome is superior to echocardiography. "Therefore," Saenger said, "an MRI is the method of choice for all patients past the age of 10 years."

Carolyn Bondy, MD, chief of the Developmental Endocrinology Branch, National Institute of Child Health and Human Development and primary investigator of the National Institute of Health Longitudinal Turner Study, said that "recent studies screening girls and women with Turner syndrome using cardiac MRI have found significant cardiovascular abnormalities that were not detected on routine transthoracic ultrasound, and for this reason it is now recommended that all individuals with Turner syndrome have a screening MRI, especially before attempting pregnancy.

"Moreover, in assessing ascending aortic diameter to estimate if the individual is at increased risk for aortic dissection, it is now clear that we must normalize for the small body size of many women with Turner syndrome, since women have experienced dissection at diameters in the normal range for average statured adults, but which are actually significantly dilated for their small body size," Bondy said.

Risk during pregnancy

According to a paper by the Practice Committee of the American Society for Reproductive Medicine published in Fertility and Sterility, women with Turner syndrome may have a 2% or higher risk for aortic dissection or rupture during pregnancy, and their risk for death may be increased as much as 100-fold.

Based on these figures, the committee recommends the screening and surveillance of women with Turner syndrome for cardiovascular irregularities. According to their recommendations, optimal surveillance of women with Turner syndrome during pregnancy includes treating hypertension and consultation with a cardiologist and periodic echocardiography. Women with aortic root diameter < 4="" cm="" may="" attempt="" vaginal="" delivery="" under="" epidural="" anesthesia,="" and="" women="" with="" baseline="" or="" progressive="" root="" dilation="" should="" have="" elective="" cesarean="" delivery="" prior="" to="" the="" onset="" of="" labor="" under="" epidural="" anesthesia,="" according="" to="" the="" committee.="">

Michael Silberbach, MD, professor of pediatric cardiology at Doernbecher Children's Hospital at the Oregon Health and Science University, expressed concern that the cutoff of 4 cm was too high for women with Turner syndrome, given their smaller size.

The Turner Syndrome Study Consensus Group made suggestions in their guidelines as well.

"Before contemplating spontaneous or assisted pregnancy, individuals with TS need a complete medical evaluation," the group wrote. "Particular attention should be paid to the cardiovascular system, and echocardiography, ECG, and MRI need to be performed before any attempt at pregnancy."

The guidelines listed a number of contraindications for pregnancy, including history of a surgically repaired cardiovascular defect, bicuspid aortic valve, evidence of aortic dilatation (>3 cm) and systemic hypertension.

Aortic dissection registries

The Turner Syndrome Society of the United States has created the International Turner Syndrome Aortic Dissection Registry. (Click here to access the registry.) This registry is a means for patients, family members and friends to report cases of aortic dissection in Turner syndrome.

"We're asking family members and friends to register people that have had dissections so we can begin to establish a profile and get the information about EKGs, blood pressure and comorbid factors that are probably contributing to the risk so that we can try to identify patients who are at a higher risk," said Silberbach, who is also on the medical advisory board of the Turner Syndrome Society.

Aortic dissection is also a well-known risk factor for patients with Marfan syndrome. According to Silberbach, much is known about the natural history and profile of aortic dissection in these patients. With that, questions arise as to whether the defects of the vascular system in Turner syndrome could be similar to those seen in patients with Marfan syndrome.

"The thought is that there is an intrinsic abnormality of the vasculature in individuals with Turner syndrome like in individuals with Marfan syndrome that causes different vascular abnormalities — such as aortic dissection and dilation and some of the other vascular abnormalities that they have found," said **Melissa Loscalzo, MD,** assistant professor in the department of pediatrics, division of genetics, at the University of South Florida.

According to Saenger, vascular abnormalities include dilation of other large vessels. "This is not limited just to the aorta," he said. "Gravholt showed in a paper that other large vessels, like the carotid and brachial artery, were wider."

Compilation of aortic data

Additional data characterizing aortic valve disease and its prevalence, along with studies examining the make-up of the aorta in patients with Turner syndrome, provide insight into the issue at hand.

Julia E. Ostberg, MD, et al compared 93 women with Turner syndrome with 25 normal controls and 11 women with 46,XX primary amenorrhea. The researchers hypothesized that genetic factors or estrogen deficiency may cause a defect in the arterial wall of patients with Turner syndrome; data from the study were published in the Journal of Clinical Endocrinology and Metabolism in 2005.

Intima media thickness was greater in women with Turner syndrome compared with normal controls (0.61 mm vs. 0.55 mm). However, the increase was similar between Turner syndrome and 46,XX primary amenorrhea (0.60 mm). The similarity "suggests that estrogen deficiency contributes to intimal thickening," the researchers wrote.

Carotid artery thickness and brachial artery diameter were also greater in Turner syndrome (5.71 mm and 3.29 mm) compared with normal controls (5.27 mm and 3.06 mm). Carotid artery diameter was independently associated with Turner syndrome status, weight, height and carotid intima media thickness, according to the researchers.

In 2007, a paper published in Circulation provided important data on aortic size among patients with Turner syndrome. **Lea Ann Matura, PhD,** et al examined aortic diameters measured by MRI in women with Turner syndrome from the NIH Turner Syndrome genotype-phenotype protocol.

Using MRI, the researchers measured ascending and descending aortic diameters in 166 women with Turner syndrome and 26 healthy controls. Women with Turner syndrome had greater ascending aortic diameters normalized to body surface area compared with controls. Ascending and descending diameter were also greater in women with Turner syndrome.

Based on their findings, the researchers recommended patients with dilated ascending aorta at an aortic size index >2.0 cm/m^2 should receive close cardiovascular monitoring. "Those with aortic size index $\geq$2.5 cm/m^2 are at highest risk for aortic dissection."

Earlier this year, a prospective study examining the prevalence of cardiac abnormalities and aortic root dilation was published in the Journal of the American College of Cardiology in 2008. In the paper, **Vandana Sachdev, MD,** et al, reported that 74 of 250 individuals with Turner syndrome (aged between 7 and 67 years) had bicuspid aortic valve.

According to the researchers, the primary cause of abnormal valves in patients with Turner syndrome (over 95%) was fusion of the right and left coronary leaflets. In patients with biscuspid aortic valve, ascending diameters were higher at the annulus, sinuses, sinotubular junction and ascending aorta. Patients with bicuspid aortic valve had higher rates of aortic root dilation compared with patients with tricuspid aortic valve (25% vs. 5%).

Need for comprehensive care

Cardiovascular risks of Turner syndrome are just a part of the landscape of ophthalmological and otological problems, absent or delayed puberty, and psychosocial and psychosexual development that come with the disease. For this reason, it is crucial that girls and women with Turner syndrome receive comprehensive care to improve quality of life. The Turner Syndrome Consensus Study group suggested that the pediatric care team consist of specialists in pediatric endocrinology, audiology, genetics, cardiology, dermatology, development, nephrology, occupational therapy, ophthalmology, orthopedic surgery, otolaryngology, psychology and speech therapy.

The implementation of a multidisciplinary team would help to ensure that patients are continuing to receive the care they need as they grow.

David E. Sandberg

"Specialized Turner syndrome clinics that provide these comprehensive services are being conducted, for example, in the Middlesex Hospital in London by Professor Gerard Conway. These clinics should serve as models for Turner syndrome centers in the United States where transition from pediatric to adult care is often still problematic," Saenger said.

David E. Sandberg, PhD, associate professor and director of the division of child behavioral health at the University of Michigan Medical School, agreed.

"It requires a team of professionals — neither endocrinologists, other specialists nor pediatricians can do it alone. One really needs to have an interdisciplinary team," he said. "The optimal approach involves effective communication among all clinicians. Each would reinforce the message of the other because good outcomes can't be achieved by focusing on only one aspect of Turner syndrome. The patient and family need to be at the center of discussions. It's important that the patient sees all the clinicians working together, as a team. One essential member of this network would be a behavioral health expert to address the predictable psychosocial and educational challenges these girls, and later women, face."– *by Stacey L. Adams and Evan Young*

FAST FACTS

Issues of Concern

1 Endocrinologists may not play a part in treating certain cardiovascular conditions among patients with Turner syndrome, but aortic dissection is among the major concerns of the disease.

2 Clinical practice guidelines for the treatment of Turner syndrome were released in 2006 by the Turner Syndrome Consensus Study Group. These guidelines include current thinking on cardiovascular disease and the best methods of handling aortic dilation, dissection and rupture.

3 The Turner Syndrome Society has created the International Turner Syndrome Aortic Dissection Registry as a means for family members and friends to report cases of the disease. Clinicians hope this provide a means for gathering more information about the risks for aortic dissection in the population of patients with Turner syndrome.

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