National Centers Needed to Aid Transition in Turner Syndrome

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COPENHAGEN, Denmark — Improvements are needed in the transition of care from pediatrics to adult services in girls with Turner syndrome (TS), because recent studies have shown that there is "hidden morbidity" that goes undiagnosed in this condition, says one expert in the field. He believes the key to better care in TS "is the establishment of at least 1 national center dedicated to the care of patients in each country around the world."

"Lifelong follow-up and screening is necessary in Turner syndrome, and we think it's inadequate at this point; there is a high dropout rate, some patients are simply lost in transition from pediatric to adult care," Claus Gravholt, MD, from Aarhus University, Denmark, told the 2013 European Congress on Endocrinology earlier this week.

"We have learned a lot over the past 10 to 15 years, [including the fact] that most Turner's patients do very well in society and get a good education and so on," but this will be jeopardized if individuals are not cared for properly, he stressed. "Recommended care needs to be implemented more often in girls and adults with Turner syndrome; it's far from optimal."

A recent Dutch study has shown that doctors diagnosed, on average, 1.2 diseases linked to TS, but after more thorough follow-up was instituted — including screening for a number of known related conditions — disease burden increased to a mean of 3.5 conditions per patient, Dr. Gravholt told the meeting.

Additional morbidity that can be missed if proper screening is not instituted includes: congenital heart disease, hypertension, hyperlipidemia, obesity, and type 2 diabetes (all cardiovascular risk factors), hearing loss, osteoporosis, hypogonadism and infertility issues, liver function, thyroid status, and screening for celiac disease. "If such issues are overlooked in adolescence, this signals a much lower quality of life in adulthood," he explained.

"Window of Opportunity" for HRT; Estrogen Essential

TS is a disorder in females characterized by complete or partial absence of an X chromosome in association with typical phenotypic features. Short stature and ovarian failure are the most prominent characteristics, but affected girls have a wide range of medical problems, including cardiac, renal, otologic, skeletal, and metabolic issues. Expert consensus guidelines on the treatment of TS were published in 2007 (*J Clin*

Endocrinol Metab. 2007;92: 10-25) and have helped guide therapy since then, but they are not being implemented in many places, Dr. Gravholt told attendees.

And although he acknowledged that much remains unknown regarding management of this condition and more clinical-trial evidence is needed, application of this existing guidance should help improve the care of these patients, he stressed.

One major issue that still causes confusion is the timing of hormone-replacement therapy (HRT) with regard to prior growth-hormone treatment, he noted.

"There have been some changes in paradigm. Earlier on, we said to delay puberty to focus on final growth velocity and final height, but growth-hormone trials have shown us this is not necessary," he explained. "If we treat people with recommended growth-hormone doses, we should not be afraid of losing centimeters. So today, we state that HRT should not be postponed until age 14 or 15 because of height issues. The recommendation in the 2007 guidance is that HRT should start at age 12 or younger, as opposed to age 14 previously."

But there are still some unknowns. "We don't know from evidence-based literature what is the optimal dose [of HRT] for pubertal induction, during early adulthood, or during the middle years and when to stop."
Treatment is generally instituted from 12 years of age, the normal age of menarche, to 52 years of age, the normal age of menopause, he noted. "We give 2 mg of 17 beta estradiol, either orally or transdermally. We gradually increase the dose of estrogen over 3 to 4 years until either breakthrough bleeding or until we think it's wise to add a gestagen to induce normal menstruation. Then a gestagen is added, but there is no research on which one is more optimal; you can use an intrauterine device [IUD] as well," he noted.

"When patients come from pediatricians they have been treated with growth hormone, and what we do is we continue the sex hormone treatment that was often started in the pediatric ward," he said. But "some patients are still not treated with HRT despite recommendations to do so."

But estrogen is essential, because of its multifactorial effects. It has benefits for bone mineralization (preventing osteoporosis) and positive effects on blood vessels (reducing BP and preventing atherosclerosis); influences cognitive function; lowers liver parameters, which are very often elevated in Turner syndrome; improves dispensability of the aorta; and affects breast growth, uterine size, and subsequently sexuality, he explained.

And uterine size is particularly important nowadays, because "we used to say, basically you are infertile," but now "a lot of patients today will be able to have egg donation and have a child." One study of just over 100 egg-donation pregnancies in women with TS showed that although a number of problems occurred during the pregnancies — some

gestational hypertension, preeclampsia, diabetes — there are generally good outcomes, he noted.

Care Better if Endocrinologists Involved

Dr. Gravholt said cardiovascular-disease risk factors are another important issue in TS patients, and a few studies have shown improved cardiac surveillance following the publication of the 2007 guidance.

"Cardiovascular disorders really take up a large chunk of the excess mortality that we see in Turner syndrome," he noted. Many patients have elevated blood pressure, hyperlipidemia, and diabetes and are obese, and it is necessary to see patients at least once a year to check BP and lipids, perform imaging studies on the heart, and generally give lifestyle advice, he said.

Other important issues that need attention include tests for thyroid dysfunction, celiac screens, osteoporosis surveillance, and hearing status; "we want to get rid of excess mortality due to other causes as well."

Studies have also shown, he said, that TS patients tend to be followed up more thoroughly if their physician is an endocrinologist and they attend large medical centers. "That's why we recommend that you have 1 or more national TS clinics; these are dedicated and should lead to implementation of international guidelines on a national basis," he concluded.

Dr. Gravholt has reported no relevant financial relationships.
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