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Females with Fabry: More Than ‘Just Carriers’

Announcer:
Welcome to ReachMD.

This medical industry feature is titled “Females with Fabry: More Than ‘Just Carriers’”. This program is intended for US healthcare professionals only and contains promotional content prepared in part by, and is sponsored by, Sanofi Genzyme.

Here’s your host, Dr. Jennifer Caudle.

Dr. Caudle:
Fabry disease is a progressive life-threatening disorder that can silently progress for years before patients present with clinical symptoms. On today's program, we'll discuss why early diagnosis is so crucial for patients, particularly women who are not just carriers of the disease, and can suffer significant complications. We'll also take a look at assessment methods that can help monitor the progression of Fabry disease in females once identified early.

Dr. Caudle:
This is ReachMD, and I'm your host, Dr. Jennifer Caudle. And joining me today for this in-depth discussion on Fabry disease is Dr. Eric Wallace. He's an Associate Professor of Medicine in Nephrology and serves as the co-director of the UAB Fabry Disease Clinic, Medical Director of Telehealth, and Director of the UAB Home Dialysis Program at the University of Alabama at Birmingham.

Dr. Wallace, thanks so much for being here today.

Dr. Wallace:
Thanks for having me. I’m excited to be here.

Dr. Caudle:
Well, we're excited to have you. So to start, Dr. Wallace, can you give us an overview of what we should know about Fabry disease? And are there any particular differences in what's observed between male and female patients?

Dr. Wallace:
Absolutely, Fabry disease is a rare genetic disorder caused by mutations in the alpha galactosidase, or GLA, gene, which results in either partial or complete deficiency of the alpha galactosidase A enzyme. This deficiency leads to progressive accumulation of glycosphingolipids. Specifically, globotriaosylceramide, or GL3, in the lysosomes of numerous cell types leading to impaired cellular function in multiple organs.

Dr. Wallace:
Fabry disease affects men and women differently. I want to begin by stating that Fabry disease is an X-linked disorder that affects both males and females. In fact, since females are not “just carriers,” they can experience significant organ damage even with minimal symptoms. In females with each cell containing two X chromosomes, one is “inactivated” through a normal, but random process called X inactivation. It's when tissue is dominated by cells with activated X chromosomes containing pathogenic GLA variants that these females present with Fabry disease symptoms. Even though some women may not present with classical early signs, all women with pathogenic GLA variants may still be at risk for severe complications in specific organ systems.

Fabry disease in females can be very complicated. When we can have females with classic mutations that don't have many symptoms, and we can also have females with classic mutations that do have a lot of symptoms. Even with sisters, with the exact same mutation, you may have one that's classic, and one that's not.

Dr. Caudle:
And as I understand it, Dr. Wallace, accumulation of GL3 is a hallmark of Fabry disease and has downstream impacts on organ systems. Is that right? And are there any signs and symptoms more commonly seen in female patients? And can this disease be life threatening for this patient population?

Dr. Wallace:
That's correct. GL3 accumulation is the hallmark of Fabry disease. And with the accumulation beginning in utero, early symptoms can progress to life-threatening complications such as kidney failure, heart failure, early stroke, or premature death. In addition to other symptoms which can negatively impact quality of life, over the course of ones lifetime, this buildup can irreversibly cause damage to three vital organs, the brain, the heart, and the kidneys.

In the brain, patients can develop white matter lesions. Patients can also get early onset of stroke, where early onset means a stroke before the age of 50. With the heart, patients are at risk of a arrhythmias and cardiomyopathy which can lead to heart failure. With regards to the kidney, a patient with Fabry disease can get chronic kidney disease, which can lead to dialysis and eventually the need for transplantation.

So those are the big ones. And unfortunately, for these vital organs, damage may not be seen with the naked eye. And as such, organ damage may go unnoticed without monitoring.

Now there are some things that may not cause life-threatening complications, but they are quality of life altering. For most patients with Fabry disease, the first symptoms might be pain in the hands, feet, or stomachs. Males can present with neuropathic pain as early as the age of 7. My patients have described that pain like a burning sensation. As an example, some have worn gloves to drive because the steering wheel felt too hot to touch, or a drink felt too cold to grab from the fridge. The pain can be so bad that they may not even get out of bed. A few other symptoms include inability to sweat, diarrhea, constipation, and reddish or purple spots on the skin called angiokeratomas.

Fabry disease can absolutely be life-threatening in females and unfortunately for reasons we don't quite understand, the cardiac involvement seems to be a common primary manifestation. Female patients can present with chest pain, arrhythmias, and heart failure. We have a lot of females who we've identified with kidney disease. But on average, the progression of kidney disease is much slower in females. There are exceptions of this. Females with Fabry disease present with pain, GI issues, but the cardiac involvement is what really concerns me.

Dr. Caudle:
Hmm, understood. So, Dr. Wallace, keeping this background understanding in mind and knowing that Fabry disease can progress silently, what can we do to get ahead of this progression?

Dr. Wallace:
With Fabry disease, diagnosis is crucial. Let's start with the low-hanging fruit first, which is that if the patient has a family member with Fabry disease, he or she needs to get screened whether or not they have symptoms. If we can diagnose patients, there are treatments out there that we can use to help manage the disease, we can do something.

The other thing to keep in mind is that the main organs like kidneys, the brain, and the heart don't show manifestation of the disease right away, not until the disease has progressed and then there could be major problems. And this is exactly why we need to monitor so we can plan and manage for when there are symptoms.

Dr. Caudle:
Well, staying on that diagnostic track, Dr. Wallace, what are some keys to incorporating diagnostic testing for a rare inherited disorder like Fabry disease? And how does this differ in male and female patients?

Dr. Wallace:
Actually, testing for Fabry disease is simple. It can easily be incorporated into standard clinical practice. So the first thing is to have Fabry disease in your differential diagnosis. So in affected males, an alpha galactosidase A enzyme assay indicating low alpha galactosidase A activity confirms Fabry disease diagnosis.

However, in female patients, GLA gene sequencing is required to confirm the diagnosis. Since because of the X inactivation, females can have normal enzyme activity despite having a mutation in the GLA gene. Gene panels used to diagnose unexplained CKD and hypertrophic cardiomyopathy may also be incorporated into the practice to diagnose Fabry disease.

Dr. Caudle:
So now, Dr. Wallace, let's talk a bit more about the impacts of missing an early diagnosis. You know, we've spoken generally to this

point about time being of the essence, given the progressive nature of the disease, but how does that translate into outcomes, specifically for female patients? And are females just carriers?

Dr. Wallace:
Time is of the essence when we talk about diagnosing patients for the Fabry disease. The impact of undiagnosed and unmanaged disease can reduce life expectancy and importantly, reduce quality of life. Vital organs, like kidneys, heart, and brain once damaged are not going back to normal as before the damage occurred. So that's why we need to screen people earlier and start managing their disease sooner, as opposed to waiting until they're symptomatic and progressing to a point of no return.

And to answer your second question, no females are not “just carriers.” There are females that are every bit as severe as males with neuropathic pain, corneal patterns in the eye, proteinuria, abdominal pain, diarrhea, and angiokeratomas. But there are also females that are much less severe.

Dr. Wallace:
When compared with females in the general population, women have a greater occurrence of left ventricular hypertrophy, stroke, TIA, white matter lesions, and end-stage renal disease. If we can identify them earlier, we can manage the disease better.

Dr. Caudle:
And considering the inherited nature of this disorder, I take it there are benefits to identifying patients quickly in the course of the disease. Is that correct?

Dr. Wallace:
Absolutely. An early diagnosis can translate into identifying other affected family members. Since Fabry disease is genetic, parents can pass it down to their children so family screening could be extremely helpful here. For every one person that diagnosed with Fabry disease, there could be an average of five additional affected family members that could be identified. If we educate family members on the inheritance pattern of this disease, and they are open to be - being tested for Fabry, this may help provide answers for patients who have been seeking a diagnosis for unexplained symptoms they've experienced in the past. Getting diagnosed earlier can help lead to earlier disease management.

Dr. Caudle:
Now, Dr. Wallace, can you share some thoughts on monitoring and modes of assessment we should keep in mind for maintaining consistent track of these patients? And when it comes to managing female Fabry patients, do you have any recommendations to help them stay consistent with coming to the clinic for regular monitoring and checkups?

Dr. Wallace:
Yeah, so regular assessments and monitoring of symptoms are keys to evaluating and managing patients with Fabry disease. Every patient with Fabry disease needs to be monitored regularly for signs and symptoms because that's how we can identify new and worsening signs and symptoms and really manage progression of the disease.

We need to monitor their kidneys to make sure their kidney function is not declining. And we can do that by checking a serum creatinine and glomerular filtration rate and a protein in the urine. In the brain, we can do a cranial MRI at least every three to five years to monitor for progression of white matter lesions. For the heart, we can do Holter monitoring at least every one to three years depending on how severe the disease is.

Just as important is cardiac imaging with an echocardiogram or cardiac MRI. One other monitoring that we do is disease specific and is done on a routine basis, and that's the monitoring of Lyso-GL3, as well as GL3.

Dr. Wallace:
And specifically for my female patients, I make sure that they understand they are not just carriers, that they have a disease that needs to be monitored. I discussed with them how Fabry disease is affecting the brain, heart, and kidneys and help them understand that monitoring is important to keep an eye on the progression of the disease. Because even knowing that the disease's progressing can help us plan for the future. Whether or not the patient is on therapy, they should still be monitored routinely.

Dr. Caudle:
And finally, Dr. Wallace, how would you encourage especially those patients who live in more rural areas who may not have a Fabry expert such as yourself nearby, you know, how would you suggest that they keep up with monitoring?

Dr. Wallace:
As the Medical Director of Telehealth at my institution, I follow a lot of patients of mine over telehealth, I think every single Fabry patient should have access to a specialist. There are many websites where you can identify Fabry specialists. Once identified, contact them and

see if they offer telehealth visits. And if they do offer telehealth visits, they can look over labs and send a monitoring plan to the patient's primary care provider. At least once a year, patients should meet with a Fabry disease specialist who really understands the disease and can monitor their disease progression. I think telehealth is a way to bridge the geographic divide that we have with patients who may not have access to these experts.

Dr. Caudle:
Well, that's a great overview of practical takeaways we can use to better recognize, diagnose, and monitor patients with this severe disease. I'd like to thank my guest, Dr. Eric Wallace for enhancing our understanding of Fabry disease. Dr. Wallace, it was wonderful speaking with you today.

Dr. Wallace:
Thanks for having me, really appreciate it.

Announcer:
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MAT-US-2106794-v1.0-10/2021