

Transcript Details

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How Can We Prevent the Delayed Diagnosis of Type 1 Gaucher Disease?

Announcer:

Welcome to ReachMD. This medical industry feature, 'How Can We Prevent the Delayed Diagnosis of Type 1 Gaucher Disease?' is sponsored by Sanofi Genzyme. This program is intended for physicians. The views and opinions included in this medical industry feature belong solely to the guests and do not reflect the view of their respective institutions.

Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:

Due to its wide range of presentations, Gaucher disease can be challenging and complicated to diagnose. Signs and symptoms vary, from spleen and liver enlargement to low platelet counts, anemia, and bone involvement. And this brings certain diagnostic challenges to light, as patients may visit various specialists when seeking an accurate diagnosis. This and other priorities will be the focus of today's program.

This is ReachMD, and I'm your host, Dr. Jennifer Caudle. Joining me today to share new insights on suspecting and diagnosing type 1 Gaucher disease as early as possible, are Drs. Coy Heldermon and Heather Lau. Dr. Heldermon is a practicing oncologist and Associate Professor of Medicine at the University of Florida. He founded the Pediatric and Adult Lysosomal Storage Disease Multidisciplinary Clinics at University of Florida. He's a member of the American Society of Clinical Oncology, and does translational research, and gene and stem cell therapies for lysosomal storage diseases. It's wonderful to have you on the program today, Dr. Heldermon.

Dr. Heldermon:

Thank you for having me.

Dr. Caudle:

Of course. And Dr. Lau is a board-certified neurologist in the Department of Neurology at the NYU Grossman School of Medicine, where she serves as director of the Lysosomal Storage Disease Program and Associate Director of the Division of Neurogenetics. Welcome to you, Dr. Lau.

Dr. Lau:

Thank you, it's great to be here.

Dr. Caudle:

Well, we're excited that both of you are here today. And Dr. Lau, we're going to start with you. Um, so to start us off, can you give us a brief refresher on what Gaucher disease is?

Dr. Lau:

Sure. Well, Gaucher disease is a rare, genetic disease in the lysosomal storage disorder's family, that causes the accumulation of a substrate called glucosylceramide, or GL-1 for short. That occurs in the cells of the monocyte and macrophage lineage. It leads to progressive, multi-organ dysfunction. It's also the most common lysosomal storage disorder disease. The hallmark signs are splenomegaly, anemia, and thrombocytopenia, which are among the most prominent and frequently presenting symptoms of type 1 Gaucher disease. But keep in mind that some patients may be asymptomatic, despite having significant disease manifestation, such as cytopenia, splenomegaly or bone involvement including bone infarcts, bone marrow infiltration and reduced bone density, like osteopenia and osteoporosis. So clearly, this constellation of signs and symptoms can present a lot like certain malignancies, which

often puts patients in front of oncologists to rule in or rule out cancer diagnoses. But patients with Gaucher disease can also run through a gamut of other specialists and diagnostic workups, trying to identify this condition as well. For example, children may first present to their pediatrician or family medicine doctor with delayed growth, or symptoms of fatigue and bruising, due to anemia and thrombocytopenia, respectively. Adult patients may get seen by GI doctors, or hepatologists, for evaluations of distended abdomens or an enlarged liver and spleen, while others may end up at the orthopedist's office for bone pain or fracture. Even asymptomatic couples, exploring family planning, can get on our diagnostic radar when seeing a geneticist or genetic counselor. But it's important to note that as we're learning more about this rare disease, we're seeing an association between Gaucher disease and an increased risk of developing hematologic malignancies, which is serious and concerning. So, this is why we encourage many specialists to think of Gaucher disease if they can't find the root cause of their patient's signs and symptoms, and to include this condition in their diagnostic workup and testing, or at least include Gaucher in genetics panels, where possible.

Dr. Caudle:

Thank you for that. Now Dr. Heldermon, turning to you, and taking into account what Dr. Lau just mentioned, we know that hematologist oncologists like yourself play a pivotal role in identifying and diagnosing these patients. So can you walk us through how you rule out, test for, and diagnose Gaucher disease?

Dr. Heldermon:

Sure. Gaucher is a serious disease. Um it's got long-term implications, if it's left undiagnosed and unmanaged, but it's manageable. We have multiple treatments available. It's important to include the Gaucher enzyme test in the differential workup. A blood-based assay measuring the activity of the lysosomal enzyme beta-glucosidase, or glucocerebrosidase, is the gold standard for a definitive diagnosis of Gaucher disease. Molecular testing can then be used to confirm the mutation and the type of Gaucher disease, as well as, uh, carrier status. While bone marrow biopsy continues to be an important part of ruling out a malignancy, or comorbid malignancy, this is not necessary, nor sufficient, uh, for diagnosing Gaucher disease. So if this disease is on your diagnostic radar, you'll want to start with the enzyme assay as part of the differential workup. Keep in mind, type 1 Gaucher disease prevalence differs among patient populations, so our diagnostic workup should take into account the patient's family history. For instance, any patient of Ashkenazi ancestry, presenting with splenomegaly or thrombocytopenia, a test for type 1 Gaucher is a first-line investigation. For all other patients, uh, you would test for type 1 Gaucher after ruling out other malignancies.

Dr. Caudle:

Okay. And Dr. Lau, coming back to you, as we focus on diagnostic challenges. What are some of the downstream consequences that can stem from a missed or delayed diagnosis?

Dr. Lau:

Well, for Gaucher disease, a missed diagnosis can result in a treatment delay for up to ten years, which obviously increases the chances of symptomatic disease progression and can lead to irreversible damage. Let's start with the skeletal impacts, since these are often the most debilitating for patients with Gaucher disease type 1. So 94% of patients in the Gaucher Registry, which is the largest confidential database of Gaucher statistics in the world – 94% of the patients have radiologic evidence of bone disease at diagnosis. Many patients present with bone marrow infiltration, Erlenmeyer flask deformity, and pathologic fractures. And as the disease progresses, patients can develop focal lytic or sclerotic lesions, um, develop joint collapse with secondary degenerative arthritis, and others can suffer from bone crises, which are episodes of deep bone pain, often with fever and leukocytosis. There are also neurologic complications secondary to bone disease, um, such as in the setting of osteoporosis, which leads to vertebral compression, can result in spinal stenosis, or even in a long bone fracture resulting in emboli, but keeping in mind that symptoms of bone pain and pathologic fractures are also associated with bone malignancy, which a bone marrow aspirate can rule out. So, as we also collect more data, we're seeing that patients with Gaucher disease also have an increased risk of developing serious neurologic conditions, such as Parkinson's disease, in both themselves, or even in their family members. So bone damage aside, as the disease progresses, patients can experience progressive visceral enlargement in the spleen and liver, alongside hepatic, splenic and marrow fibrosis.

Children can experience growth failure. Lung disease and pulmonary hypertension are potential complications. And of course, bleeding and associated bleeding complications, such as anemia, fatigue and pallor can develop. Now clearly, given these potential multi-organ impacts, Gaucher disease can have profound effects on a patient's quality of life, and the disease progression itself increases risk of cancer, so this can be a condition that significantly shortens lifespan. But like Dr. Heldermon said earlier, this is a manageable disease, and there are multiple treatments available. So regardless how patients present, in terms of signs and symptoms, or severity, it's extremely important to diagnose them as soon as possible, to initiate timely treatment.

Dr. Caudle:

Thank you for that! And for those of you who are just tuning in, you're listening to ReachMD. I'm your host, Dr. Jennifer Caudle, and

today I'm speaking with Doctors Coy Heldermon and Heather Lau about Gaucher disease type 1 and the imperative to suspect and early.

So, we've gotten a better sense of the downstream impacts when the diagnosis is delayed or missed, but I want to come back to the genetic factors associated with this disease. Dr. Lau, can you expand on the inherited pattern of Gaucher disease and the populations groups that are more susceptible to it?

Dr. Lau:

So, Gaucher disease is an autosomal recessive genetic disorder that affects males and females equally. It's pan ethnic, with an instance of about 1 in 40,000. But we do see higher incidences in individuals of Ashkenazi Jewish descent. In this population, the incidence is about 1 in 850, which, to give you a frame of reference, is much more common than the incidence of hematologic malignancies in the broader population, which is about 1 in 2,500. And as you may know, 90% of Americans Jews are Ashkenazi, so this is a significant patient population. So, in this ethnic group, it's prudent to test for Gaucher disease, as a first-line investigation in any patient presenting with splenomegaly and cytopenia. It is also important to keep in mind that most, the most common mutation in this population is the N370S variant, now known as N409S, and though most patients with this mutation are asymptomatic, they can experience adult-onset disease, with a disproportionate burden of progressive skeletal disease, with or without major visceral or hematologic involvement. In fact, patients with homozygous N370S mutations often develop characteristic signs of mild cytopenia and splenomegaly that can escape initial detection. Lastly, because of these inheritance patterns, family screening becomes especially important, to identify others who are at risk. Remember that it's common for patients to go undiagnosed for years, while their disease is silently progressing, so consider the family alongside each patient.

Dr. Caudle:

Thank you. And Dr. Heldermon, coming back to you, in our final minutes, what are some of your priorities as an oncologist, in regards to Gaucher disease, that you'd like to share with our audience?

Dr. Heldermon:

Well, I'll reiterate that oncologists, such as myself, do play a pivotal role in identifying and diagnosing these patients. They most often come to us, medical history suggestive of cancer, so we have a responsibility to keep Gaucher disease in mind. The same need for awareness and recognition extends to the other clinicians we talked about, such as pediatricians, family medicine doctors, primary care doctors, gastroenterologists, orthopedists, genetic counselors. Strongly urge these groups to keep Gaucher disease in mind as well, because the patients may come to them first. It's important to rule out malignancy and test for Gaucher disease in patients who present with splenomegaly and anemia and thrombocytopenia, especially for patients of Ashkenazi descent, um, in whom you'd want to test for Gaucher first, or simultaneously, because we know it's that much more common in this population. And absolutely, we have to be proactive about testing for this disease, because it's easy to do, with a simple assay that's available in most commercial labs. I can't emphasize enough that because it is a manageable disease, if it's left undiagnosed or unmanaged, Gaucher can progress into a very serious disease, with long-term consequences.

Dr. Caudle:

And Dr. Lau, what are some parting thoughts you'd like to share with our listeners?

Dr. Lau:

Thank you. I completely agree with Dr. Heldermon on this, whether you're a generalist or a specialist, Gaucher disease needs to be on your diagnostic differential, given its extreme variability and phenotype, age of onset and disease severity. The disease course is progressive, but the progression can be highly unpredictable. So it's critical to diagnose Gaucher disease as soon as possible, to get effective treatments onboard quickly. And as I had mentioned earlier, from my point of view as a neurologist, although individuals with type 1 Gaucher disease don't have primary CNS disease, neurologic complications do occur, and they include Parkinson's disease, in the patient themselves or their – even in their family members, as well as spinal cord or nerve root compression secondary to bone disease. So these are some of the signs and symptoms I may be looking at, that make me suspect Gaucher if I can't find another cause. And we've talked about the challenges in diagnosing Gaucher disease based on the variability, and overlap in how symptoms present. That's why I come back to the idea that whether you're assessing patients from a neurologist's, oncologist's, or generalist's framework, if you can't find the cause of your patient's signs and symptoms, consider testing for Gaucher, even before you refer them, because it could drastically shorten the diagnostic journey for these patients.

Dr. Caudle:

Well, you both have given us great new vantage points on that diagnostic journey, so with that, I'd like to thank you both for sharing your insights in type 1 Gaucher disease, and the key roles that clinicians across medical and surgical disciplines can play towards earlier

recognition, testing and diagnosis. Dr. Heldermon and Dr. Lau, it was great having you both on the program today.

Dr. Heldermon:

Thank you.

Dr. Lau:

Thank you.

Announcer:

This medical industry feature has been sponsored by Sanofi Genzyme. For more information on the diagnostic and therapeutic landscape for Gaucher disease, including access to Sanofi Genzyme Rare Disease Registries, visit [Gauchercare.com/hcp](https://www.gauchercare.com/hcp). And to check out additional content focusing on Gaucher disease, visit ReachMD.com. This is ReachMD. Be Part of the Knowledge.