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Closing Gaps in the Recognition & Detection of Niemann-Pick Disease Type C

Announcer:
Welcome to ReachMD. This medical industry feature, titled, “Closing Gaps in the Recognition & Detection of Niemann-Pick Disease Type C” is sponsored by Orphazyme. This program is intended for US healthcare professionals.

Your host for this program is Dr. Jennifer Caudle.

Dr. Caudle:
Niemann-Pick disease type C or NPC is an ultra-rare[1] inherited[1], neurodegenerative disease[3] with life-threatening complications. Because of its highly variable onset of neurological symptoms throughout one’s lifespan, recognizing and establishing diagnosis for NPC can be challenging for any clinician.[2,3]

On today’s program, we will address those challenges with an in-depth look at this genetic condition, the factors underlying its variable onset and course, strategies to improve recognition and communication across specialties, and ways to improve the diagnostic speed.

This is ReachMD and I’m your host, Dr. Jennifer Caudle.

Joining me for today’s expert panel are Dr. Caroline Hastings and Dr. Raymond Wang. Dr. Hastings is a Pediatric hematologist-oncologist at the UCSF Benioff Children’s Hospital of Oakland, California.

Dr. Hastings, thanks for being here, today.

Dr. Hastings:
Thank you, so much for having me today.

Dr. Caudle:
And Dr. Wang is the Campbell Foundation Director of the Multidisciplinary Lysosomal Storage Disorder Program, a board-certified clinical geneticist, and biochemical genetics specialist at the Children’s Hospital of Orange County in Orange County, California, or CHOC.

Dr. Wang, it’s great to have you with us.

Dr. Wang:
Thank you so much for having me, today.

Dr. Caudle:
To start, Dr. Hastings, can you give us a detailed understanding of what Niemann-Pick disease type C is?

Dr. Hastings:
Niemann-Pick C is a genetic disease that’s inherited in an autosomal recessive fashion.[1] To date, there are 513 mutations[8] that have led to problems with the NPC protein, which in part, explains the extreme variability of the clinical presentation. And this variability also includes the timing of presentation from infancy to late in adulthood, as well as the clinical spectrum of manifestations, which makes this a difficult disease to identify and to diagnose early. Many patients experience a delay between the time they started having symptoms to the time of their diagnosis. In fact, some patients may not even realize that these symptoms are part of the disease, at all.

Additionally, NPC is a heterogeneous disease.[4] The clinical course and lifespan of patients with NPC varies and their phenotypic

manifestations are diverse,[4] with some of the most frequent clinical presentations including abnormalities in ambulation and gate, or frequently ataxia.[4] Infant patients, especially tend to be severely impaired often presenting from birth or within the first couple of months of their lives. They may have a combination of systemic findings, such as a very large liver and/or spleen or evidence of neurologic dysfunction.[4] Unfortunately, NPC in infants tends to progress more rapidly with earlier mortality than is seen in other groups.

In our adolescent and young adult patients, we also see some unusual manifestations, in particular psychiatric manifestations. Often, these patients may be diagnosed with a primary psychiatric disorder.[4] And they may also present with evidence of a movement disorder, which eventually leads to the diagnosis.

Dr. Caudle:
Thank you, Dr. Hastings. Now, turning to you, Dr. Wang. How does one's genetic makeup contribute to NPC?

Dr. Wang:
So as Dr. Hastings has mentioned earlier, Niemann-Pick disease type C is inherited.[1]

There are two different genes, *NPC1* and *NPC2*, which when altered or mutated, give rise to Niemann-Pick disease-type C symptoms.[9] The overwhelming majority of NPC cases, about 95%, come from changes in the *NPC1* gene, and a smaller proportion come from mutations of the *NPC2* gene.[9] Both of these proteins are thought to be involved in the efflux of cholesterol from a part of the cell called the lysosome. And so, when there are gene changes or alterations, that impair the function of either the *NPC1* or *NPC2* protein, then there's a build-up of cholesterol and other lipids within the lysosome.[11-13] This causes a cascade of deficits within the cell and ultimately results in cellular death. It's these processes that cause the multiple different organ manifestations, whether it's in the brain, the liver, the spleen, or elsewhere within the body.[4]

Dr. Caudle:
It makes sense, Dr. Hastings, why diagnosing NPC is challenging because of our earlier discussion about the varied clinical course and lifespan of NPC. What are some other factors that could be leading to misdiagnoses, delayed diagnoses, and unmet patient needs?

Dr. Hastings:
NPC is a challenging diagnosis to make for many reasons. One of those reasons is that it's an extremely rare disease,[1] so many clinicians will not have had the experience with this disease firsthand, let alone know much about what the disease is or what the manifestations may be. So, I think that despite many patients seeking medical diagnoses, it still does depend on whether they interact with a physician who's had experience with lysosomal storage disease, and in particular, NPC.

And another reason that NPC's presentation can be challenging is that it can present at different ages[1] and with varying severities and varying rates of progression that can make the diagnosis also extremely difficult.[4] I think that many of the subtle signs and symptoms of the disease may go unrecognized during an assessment. For example, many patients may have mild cognitive impairment that leads to difficulty in schoolwork and this may not be picked up on an exam and family members may just feel that that is who they are, and they are actually doing just fine, when in fact, this issue with schoolwork could be a clue that leads to diagnosis and subsequent treatment.[4]

And finally, many patients end up seeing physicians from many different specialties before the NPC diagnosis is actually reached and all of these reasons can contribute to a delay in diagnosis.

Dr. Caudle:
Well put, Dr. Hastings. Now, Dr. Wang, based on your experience, when you're talking with your patients, what are some things that perk up your ears and raise your suspicion for NPC?

Dr. Wang:
That's a great question. Thank you. So, as Dr. Hastings previously mentioned, some of the most frequent clinical manifestations of NPC include abnormalities in ambulation and gate, frequently ataxia, but there could also be more subtle or even more specific symptoms of the disease like vertical supranuclear gaze palsy.[4] A lot of people don't realize that this is a symptom of NPC. Also, cataplexy is an unusual symptom and ought to make you consider NPC as a diagnosis. Although not everyone with Niemann-Pick C actually ends up having cataplexy.[4]

We find that many NPC patients may have had unrecognized symptoms that date back many years, including things like being labeled as "clumsy" or a "slow learner" and needed some additional assistance in school. In those cases, NPC was not suspected, and the disease continued to progress slowly. Because of this common history of long-term symptoms, when I hear from patients who have had issues for years who have speech fluency, clarity, cognitive delays, and early onset of memory dysfunction and learning disabilities, my

mind does go to NPC.

Dr. Caudle:
That's very helpful. And staying with you, Dr. Wang, given those challenges, what are the current recommendations for detecting and diagnosing Niemann-Pick disease type C?

Dr. Wang:
Yes, that's indeed, quite a challenge. So, given all the information that we've discussed, so far, let's go through this. How can we go about identifying and confirming a diagnosis of NPC for a patient that's been referred to your office?

The first step is having a strong suspicion of NPC for a patient who has unexplained neurologic symptoms, neurovisceral symptoms, or some combination thereof.[14] Once that suspicion is present, the next step is measuring levels of various biomarkers within the bloodstream.[14] Because of the impaired cholesterol transport within cells, we can measure different markers of this lysosomal dysfunction in the bloodstream. This is a helpful first step in distinguishing whether a patient has NPC or some other condition or if they might not have an inherited disorder, at all. And so, if we find that there are abnormalities in this biomarker profile that is possibly consistent with NPC disease, the next step then will be to perform genetic testing, which would involve the sequencing of both *NPC1* and *NPC2* genes.[14] From here, since there could be many different potential outcomes with the sequencing, the simplest one we can find is what we call pathogenic or disease-causing mutations in either *NPC1* or *NPC2*, which would then confirm a diagnosis of Niemann-Pick C, disease.

If there's sufficient clinical suspicion that the patient had NPC, we would proceed with further molecular studies.[14] These may include deletion and duplication analysis because sometimes there are larger rearrangements in these genes that can't be identified by standard sequencing techniques. On the other hand, if the suspicion of NPC is high enough and these additional sequencing tests do not identify a deletion or a duplication or other rearrangement in these genes, there is an additional biochemical functional test called filipin staining,[14] which requires a sample, of skin, a skin biopsy and growth of, fibroblasts or skin cells. The laboratory will then take these, fibroblasts, culture them and determine whether those cells have abnormal cholesterol processing. If there's evidence of abnormal processing, as seen by this increased staining with filipin, then along with the prior testing performed, those would confirm a diagnosis of Niemann-Pick Disease type C.[14] If there isn't any evidence of abnormal cholesterol trafficking, that rules out a diagnosis of NPC disease.[14]

Dr. Caudle:
For those of you who are just joining us, this is ReachMD and I'm your host, Dr. Jennifer Caudle. Today I'm speaking with Drs. Caroline Hastings and Raymond Wang about the need to accelerate diagnosis of patients with Niemann-Pick disease type C.

As we've just heard from Dr. Wang about the current recommendations for detecting and diagnosing NPC, let's turn to you, Dr. Hastings, and hear your unique approach as a hematologist when considering an NPC diagnosis for a patient.

Dr. Hastings:
Sure. As a hematologist, I'm often referred patients for evaluation of hepatomegaly or splenomegaly, and often I'll also obtain a family history. And if I determine or see that other family members have also been affected, for example, with splenomegaly, my suspicion that the patient has an inherited disease goes up. As well, I do tend to seek other possible signs or symptoms that may give me clues to the disease present. And this will be looking for subtle learning problems, neurologic findings on exam and if those are present, I then start to move towards the possibility of this being a lysosomal storage disease.

I think we've had a lot of missed opportunities here, because many of our patients who may have had splenomegaly for a while have been evaluated by providers who didn't recognize NPC as a possibility. And most of us go through the whole typical workup looking for infectious or primary hematologic causes of an enlarged spleen or liver and we miss the NPC diagnosis. I've even had patients with a long-term history of splenomegaly for example even up to ten years and they haven't had a thorough workup and it was dismissed as being no big deal because the patient appeared otherwise well. There does need to be more awareness of the disease in the exam stage, as well.

Dr. Caudle:
You know, that's definitely a missed opportunity. Thank you for that, Dr. Hastings.

And Dr. Wang, as a geneticist, in your opinion, what are some communication strategies that a multi-disciplinary team could employ to speed up the diagnosis of NPC?

Dr. Wang:

Thank you very much for that question. I think we've definitely learned that communication is key. I can speak for our center at CHOC, and we work very closely with the various specialists who can serve as the first evaluators for a potential patient with Niemann-Pick disease type C. For example, we are often consulted in the neonatal intensive care unit evaluating children with cholestatic jaundice or organomegaly for metabolic disorder. So, our neonatologists are well-attuned to the possibility that visceral symptoms may include an inherited condition. We also work very closely with our gastroenterologists, who may be the first evaluators for a patient who has organomegaly, conjugated hyperbilirubinemia, or other liver-associated abnormalities. And we work with our ophthalmologists and neurologists who may be the first physicians to evaluate some of the neuro-ophthalmologic conditions that these patients present with. At CHOC, we have a child neurology and genetics collaborative clinic where the child neurologist and I see patients together. One of the most frequent conditions, we've mentioned earlier that we encounter with NPC patients in this clinic is ataxia. And so, as a result, we order ataxia gene panels that include testing for *NPC1* and *NPC2* to better characterize this heritable cause for ataxia.

So, in summary, I believe all of these collaborations tremendously facilitate a multidisciplinary communication approach, but it all starts with having an awareness of the potential symptoms and that clinical suspicion so that even if a patient with, say, organomegaly in the neonatal intensive care unit, doesn't end up having NPC disease, we still have the opportunity to educate our colleagues who will be evaluating these children. We can inform them that these children do need referrals for a metabolic evaluation, which then includes NPC disease within the differential diagnosis.

Dr. Caudle:
Again, I appreciate your insight on this, Dr. Wang. Coming back to you, Dr. Hastings, on the side of therapeutic considerations, have there been any clinical innovations pointing to more effective therapies in the NPC treatment landscape?

Dr. Hastings:
Yes, if you look at the last ten years, we've definitely made some significant headway, both in understanding the nature of the disease and in understanding that even though the NPC protein is very complicated, and we've yet to get to the bottom of everything it does, we do understand this is a cholesterol-trafficking problem. And its unesterified form, cholesterol gets stuck in the cells and causes damage, leading to early cell death.[11-13] We know that this is especially toxic to the nervous system[2] and it's probably what directly impacts and causes a lot of the signs and symptoms that we see in NPC. But that doesn't really answer the question about why this, there's such a clinical spectrum of manifestations. There's so much more to learn about the complexity of this disease and all the factors that may play a role. There are clinical innovations that are coming out with new drugs that look at ways to deplete cells of cholesterol move cholesterol out of the cells, rearrange the configuration of the NPC protein, as well as investigate options in gene therapy, but I suspect there'll be many more innovations as we learn more about the disease itself. And given the variability we see in this disease, patients may ultimately benefit from multiple simultaneous interventions.

Dr. Caudle:
Thank you, Dr. Hastings. Before we wrap up, Dr. Wang, I'd like to open up the floor to hear your thoughts on how to improve the speed of diagnosing Niemann-Pick disease type C.

Dr. Wang:
Absolutely, Dr. Caudle. I think the availability of multiple tests to identify a patient with Niemann-Pick disease type C has been a tremendous benefit, especially compared to diagnostics five to ten years ago. It used to be that fibroblasts filipin testing was the only available test, which often took a long time, contributing to delays in diagnosis. But because we now have the availability of blood biomarkers, as well as genetic testing that include gene panels that have *NPC1* and *NPC2* within their symptoms, the ability to identify a patient with potential Niemann-Pick disease type C has become much more reliable and a lot faster. But what's really important, again, is to have NPC on your suspicion list, because early identification of the disease allows for the potential to initiate therapies sooner, which leads to slower progression of disease before it gets to a point where skills cannot be regained by the patient.

Dr. Caudle:
Excellent points, Dr. Wang. And Dr. Hastings, I'll give you the final word. What are some closing remarks you'd like to share with our listeners with regard to recognition and management of Niemann-Pick disease type C?

Dr. Hastings:
When patients present with this constellation of complex signs and symptoms, it's really important to seek subspecialty collaborations to have a collective expertise when considering a diagnosis. I also think it's important to look at all the prior assessments that may have been done by other subspecialists, that may be from neurology, neuropsychiatry, speech, or physiatry, and also examine these findings so that you really understand the scope of the disease that the patient has, and also understand if it's changing or if there's progression of these symptoms. And to echo Dr. Wang, I feel if there's a clinical suspicion of NPC, that it's important to seek consultation from somebody that may have expertise in NPC. And again, the earlier the disease is recognized and diagnosed, the sooner we can initiate

some intervention that will lead to improved outcomes.

Dr. Caudle:
Well-said. You both have shared a comprehensive background to such a complex disease, as well as several team-oriented strategies that could speed up diagnosing a patient with Niemann-Pick disease type C. With that, I'd like to thank my guests for sharing their unique clinical perspectives on improving the time to diagnosis and communication between the multi-disciplinary teams. Dr. Hastings, Dr. Wang, it was great speaking with you both, today.

Dr. Hastings:
Thank you, so much for having me.

Dr. Wang:
Thank you.

Announcer:
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