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Under the Radar: Diagnosing Hereditary ATTR Across Specialties

Announcer:
Welcome to ReachMD. This medical industry feature, titled “Under the Radar: Diagnosing Hereditary ATTR Across Specialties” is sponsored by AstraZeneca.

Here’s your host, Dr Charles Turck.

Dr Turck:
This is ReachMD, and I’m your host Dr Charles Turck. On today’s program, we’ll explore the challenges in identifying patients with hereditary transthyretin-mediated amyloidosis, also known as hereditary ATTR, and hear clinical perspectives on systematic workflows that may support earlier and more accurate diagnosis. Joining me are Drs Kevin Alexander and Anasheh Halabi.

Dr Kevin Alexander is an advanced heart failure-trained cardiologist as well as an Assistant Professor of Cardiovascular Medicine at Stanford University School of Medicine in Palo Alto, California.

Dr Alexander, welcome to the program.

Dr Alexander:
Happy to be here.

Dr Turck:
And Dr Anasheh Halabi is an Assistant Clinical Professor in the Department of Neuromuscular Neurology and Director of the Neuropathy Program at the David Geffen School of Medicine at UCLA.

Dr Halabi, it’s great to have you with us as well.

Dr Halabi:
Thanks for having me.

Dr Turck:
So, Dr Alexander, let's start with the big picture. Would you give us a sense of where things currently stand when it comes to diagnosing patients with hereditary ATTR?

Dr Alexander:
Of course. So hereditary ATTR is often under-recognized and misdiagnosed, which can lead to delayed diagnosis and poor patient outcomes.[1,2] The disease has a non-specific, multisystem presentation with seemingly unrelated signs and symptoms, so it’s easier to mistake for, or associate with, other comorbidities.[3]

We generally categorize hereditary ATTR into three clinical phenotypes: predominantly neurologic, predominantly cardiac, or a mixed phenotype that includes both polyneuropathy *and* cardiomyopathy.[4-6]

Dr Alexander:
This heterogeneity means that many patients experience multiple misdiagnoses.[2,3,7] In fact, up to 44 percent of patients are initially misdiagnosed, and nearly half report seeing three or more doctors before receiving a diagnosis.[8] These delays are substantial—the mean time to diagnosis can range from three to four years for hereditary ATTR polyneuropathy and two to seven years for hereditary

ATTR cardiomyopathy.[2,9]

Unfortunately, delayed treatment may lead to irreversible disease progression, loss of quality of life, and even death.[1,3,10-13] So by the time an accurate diagnosis is made, the median survival is five to 15 years for hereditary ATTR polyneuropathy and two to five years for hereditary ATTR cardiomyopathy.[2,4,7,9] That's why earlier recognition is so important. We may have an opportunity to slow disease progression, and we don't want to miss it.[14]

Dr Turck:
Thanks for that important context, Dr Alexander. And now turning to you, Dr Halabi, what challenges have you seen with diagnosing hereditary ATTR and how do you recommend addressing them?

Dr Halabi:
So when it comes to these ongoing challenges in identifying ATTR patients, there are definitely systemic factors that contribute.[14,15]

Sometimes there's inconsistent clinician knowledge about ATTR and a perception that it's a rare, incurable, or untreatable disease.[15] I think this perception may discourage some physicians from pursuing diagnostic workups.

Fragmented knowledge is another issue. Primary care providers and specialists may each have a piece of the puzzle, but unless those dots are connected, patients may go undiagnosed or misdiagnosed for years.[1,2,15] On top of that, the diagnostic workup can be complex for certain patients, and we're also dealing with a shortage of specialized centers for amyloidosis management.[15]

In addition, as Dr Alexander mentioned, hereditary ATTR doesn't present uniformly.[2,16] In fact, around 60 percent of patients in the U.S. present with a mixed phenotype.[17] And so patients with the disease often see physicians across multiple specialties before receiving a diagnosis.[8,11,18,19]

A survey by the Amyloidosis Research Consortium, which included 114 patients with hereditary ATTR-CM, showed that 39 percent were diagnosed by a cardiologist, 16 percent by a neurologist, and a small percentage by hematologists, internists, or nephrologists at six, five, and two percent, respectively. The rest were diagnosed by various other specialists or primary care providers.[8]

So while cardiologists are often well-positioned to identify patients with hereditary ATTR, I think neurologists could be better positioned to do so. This starts with increasing awareness and establishing clear, scalable workflows to drive early diagnosis, accelerate time-to-intervention, and improve patient outcomes.[2,9]

Dr Turck:
Thank you, Dr Halabi. And Dr Alexander, given everything we've discussed so far, would you elaborate on the symptoms that should raise clinical suspicion for hereditary ATTR?

Dr Alexander:
Absolutely. So because hereditary ATTR affects multiple systems, maintaining a high index of suspicion is key. This is especially crucial when patients present with unexplained symptoms that span across sensorimotor and autonomic neuropathy, cardiac, and musculoskeletal systems.[2,3,7,11,20-22] From my experience, one of the challenges is that these manifestations often do not appear all at once. They may emerge sequentially over years, making the broader pattern easy to miss.[3]

What's critical is to recognize when these symptoms occur together, even if they don't appear at the same time. Individually, they might point to more common conditions. But in combination, they should prompt further evaluation for hereditary ATTR.[2,3,7,11,20-22]

In some patients, extracardiac manifestations may precede overt cardiac involvement by years. For instance, a patient might first present with bilateral carpal tunnel syndrome and later develop atrial fibrillation, peripheral edema, and neuropathy. Another might have lumbar spinal stenosis, bilateral carpal tunnel syndrome, or even biceps tendon rupture before the onset of congestive heart failure.[2,3,7,11,20-22]

Or you might see a patient who's had carpal tunnel release without improvement, along with orthostatic hypotension and peripheral neuropathy. This pattern should also raise concern.[2,3,7,11,20-22]

And finally, a patient presenting with autonomic dysfunction, such as persistent, unexplained diarrhea or constipation alongside neuropathy and bradyarrhythmia, should prompt a thorough review of systems.[2,3,7,11,20-22]

These multisystem combinations and sequences are often the clues we need to help catch hereditary ATTR earlier and to potentially

change the disease trajectory for our patients.[2,3,7,11,20-22]

Dr Turck:
For those just tuning in, you're listening to ReachMD.

I'm Dr Charles Turck, and today I'm joined by Drs Kevin Alexander and Anasheh Halabi about challenges in diagnosing hereditary transthyretin-mediated amyloidosis, or hereditary ATTR, and their clinical perspectives on better identifying patients through established protocols.

So let's dive deeper now into streamlining patient identification, particularly through a more systematic approach. Dr Alexander, from a cardiologist's perspective, what does that workflow look like in clinical practice?

Dr Alexander:
That's a great question. In practice, this workflow often begins when a patient presents with cardiopulmonary symptoms or cardiac findings that raise suspicion for amyloidosis—whether that's on history, ECG, or echocardiography. Once cardiac amyloidosis is suspected, the first step is to distinguish between ATTR amyloidosis and light-chain, or AL, amyloidosis.[2,11,18,23,24] However, one survey of 46 healthcare providers found that of providers who were aware of amyloidosis, 63 percent weren't confident differentiating between the two diseases.[25]

And so I'd like to inform my colleagues that we can start by evaluating serum free light-chain ratios, alongside with serum and urine electrophoresis with immunofixation to look for monoclonal proteins. In patients with normal kidney function, a serum kappa/lambda free light-chain ratio less than 0.26 or greater than 1.65 is considered abnormal and may suggest AL amyloidosis. But it's important to interpret that result in clinical context, because the ratio can be higher in patients with renal dysfunction. Based on those results, if monoclonal proteins are detected by immunofixation, the patient should be referred to hematology—and in some cases, a cardiac biopsy may be needed to confirm AL amyloid cardiomyopathy.[18]

But if the monoclonal protein screen is negative, we move on to bone scintigraphy scans of the heart using technetium-99m pyrophosphate—also known as PYP—or hydroxymethylene diphosphonate, also known as HMDP. In the absence of monoclonal proteins, a grade two or three uptake on a bone PYP or HMDP scan is considered positive for ATTR cardiomyopathy.[18,26]

Once ATTR cardiomyopathy is confirmed, the guideline recommendation is to perform transthyretin genotyping. This step is essential to distinguish hereditary ATTR from wild-type, and it plays a critical role in guiding further treatment decisions and family counseling.[18,24,27,28]

Finally, guidelines, including those from the American College of Cardiology, recommend that if a patient is found to have hereditary ATTR, they should also be evaluated for signs of polyneuropathy. That ensures we're managing the full scope of the disease and not missing a mixed phenotype.[18]

Dr Turck:
I see. And then from a neurologist's perspective, Dr Halabi, what is the diagnostic approach look like and what steps may help us identify patients earlier?

Dr Halabi:
Sure. So in neurology, we can also apply a systematic approach to triage patients with suspected amyloidosis. The first step is a comprehensive neurologic evaluation to discern ATTR from other neuropathies. This includes taking a detailed patient history, looking for sensorimotor and autonomic symptoms, and conducting a thorough physical exam.[2,11,18,23,24]

One of the key features that sets hereditary ATTR polyneuropathy apart from more common polyneuropathies is its rapid progression, and the presence of bilateral carpal tunnel that can sometimes precede peripheral neuropathy by years.[3,29-31]

Based on expert consensus, clinicians should consider hereditary ATTR polyneuropathy in patients with idiopathic, rapidly progressive sensorimotor axonal neuropathy or atypical chronic inflammatory demyelinating polyneuropathy when accompanied by one or more red-flag symptoms. These red flags can include a family history of neuropathy, heart failure, or abnormal heart rhythm. You might also see bilateral carpal tunnel syndrome or autonomic dysfunction, and, in some cases, unexplained weight loss, gait disturbances, left ventricular hypertrophy, vitreous opacities, or nephropathy.[2]

An electromyography/nerve conduction study can be a useful part of the evaluation, particularly in patients with more advanced or progressive neuropathy, but it shouldn't be viewed as confirmatory. When abnormal, EMG/NCS typically has an axonal pattern, although there are certainly exceptions to this. It's important to remember that conventional EMG/NCS can't detect small-fiber

neuropathy and may be normal early in the disease course, especially when small-fiber involvement predominates. So a normal electrodiagnostic study should not dissuade clinicians from pursuing further evaluation when suspicion for hereditary ATTR remains high.[23,32]

So, from here, the last two steps mirror what Dr Alexander outlined earlier from a cardiology viewpoint. If the clinical picture is suggestive—and especially as the broader neuropathy workup is otherwise unrevealing—clinicians should have a low threshold to pursue transthyretin gene sequencing, because that's the key confirmatory step for hereditary ATTR. And once hereditary ATTR is identified, it's essential to evaluate for cardiac involvement as well, so we don't miss a mixed phenotype and can guide management appropriately.[2,11,18,23,24]

Dr Turck:
It's been great to hear both of your clinical perspectives on these workflows. Now before we wrap up, I'd love to give each of you a moment to share any final thoughts with our listeners. Dr Alexander, let's start with you.

Dr Alexander:
Thanks, Dr Turck. I think a key message is that we have a real opportunity to improve how we identify patients with hereditary ATTR. It starts with raising clinical awareness about multisystem symptoms.

When we observe unexplained combinations of polyneuropathy and cardiac or musculoskeletal symptoms, we need to consider ATTR as part of the differential.[2,3,7,11,20-22] From there, the diagnostic pathway should be guided by the patient's presentation. In some cases, that means first ruling out AL amyloidosis and confirming cardiac ATTR. In others, the evaluation may begin with a neurologic workup and genetic testing. Once the diagnosis is established, we can assess for a mixed phenotype to get a full picture of the patient's clinical presentation and tailor management accordingly.[2,11,18,23,24]

Building cross-specialty awareness and maintaining a low threshold to refer may also help support faster diagnosis, since many patients ultimately need collaborative care across more than one specialty.[3,14,15] And because delays in treatment may lead to irreversible disease progression, identifying patients in a timely manner is critical. The sooner we diagnose a patient with hereditary ATTR, the earlier we can intervene, and that's our chance to help preserve their function, independence, and quality of life.[1,3]

Dr Turck:
Thank you, Dr Alexander. And Dr Halabi, your final thoughts?

Dr Halabi:
Yes, I'll add that increasing disease awareness and making the diagnosis are essential first steps. From a neurology perspective, if we don't recognize hereditary ATTR, the rest of the care pathway simply doesn't happen. It's equally important to ensure patients are placed on the appropriate treatment path—one that's guided by current evidence and supported through multidisciplinary collaboration.[2,9,33]

I also think this is where scalable, systematic approaches have the potential to make a real impact on the patient journey. Structured referral algorithms, easier access to testing, and practical workflows that support evaluation in community practice can help streamline this process. Altogether, these efforts may bring us closer to more timely care and better outcomes for patients.

Dr Turck:
Excellent insights to reflect on as we come to the end of today's program. And I want to thank my guests, Dr Kevin Alexander and Dr Anasheh Halabi, for sharing their expertise and helping us better understand both the challenges and opportunities in patient recognition for hereditary transthyretin-mediated amyloidosis.

Dr Alexander and Dr Halabi, it was great speaking with you both today.

Dr Alexander:
Great speaking with you as well.

Dr Halabi:
Thanks for having us.

Announcer:
This medical industry feature was sponsored by AstraZeneca. If you missed any part of this discussion, visit Industry Features on ReachMD.com, where you can Be Part of the Knowledge.

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