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From Symptoms to Diagnosis: Navigating ATTR Amyloidosis in Clinical Practice

Announcer:
Welcome to ReachMD. This medical industry feature, titled “From Symptoms to Diagnosis: Navigating ATTR Amyloidosis in Clinical Practice,” is sponsored by AstraZeneca. Here’s your host, Dr Jennifer Caudle.

Dr Caudle:
This is ReachMD, and I’m your host Dr Jennifer Caudle and joining me today to discuss key takeaways from expert consensus publications on diagnosing transthyretin-mediated amyloidosis, or ATTR amyloidosis, are Drs Thomas Brannagan and Marcus Anthony Urey. Dr Brannagan is a Professor of Neurology, as well as the Director of both the Peripheral Neuropathy Center and the Columbia Neuropathy Research Center at Columbia University in New York.

Dr Brannagan, welcome to the program.

Dr Brannagan:
I’m happy to be here.

Dr Caudle:
And Dr Marcus Anthony Urey is an Associate Professor of Medicine as well as Director of the Cardiac Amyloidosis and Heart Transplantation programs at UC San Diego. Dr Urey, thank you so much for joining us today.

Dr Urey:
Thanks for having me.

Dr Caudle:
So let's start with you, Dr Brannagan. What are the key clinical features or symptoms that should trigger suspicion of ATTR polyneuropathy?

Dr Brannagan:
Well, that’s a great place to start because recognizing the early signs of ATTR polyneuropathy is crucial for timely diagnosis and management, and a high index of suspicion can significantly expedite the diagnosis.[1]

Key red-flag symptoms include lumbar spinal stenosis, bilateral carpal tunnel syndrome, which can typically present 4 to 6 years before other symptoms of hATTR, biceps tendon rupture, and dysautonomia, such as alternating diarrhea and constipation or orthostatic hypotension. In conjunction with peripheral neuropathy, these symptoms should prompt clinicians to consider ATTR amyloidosis. [2–5]

In endemic areas, such as Portugal, Japan, Sweden, or Brazil, patients may present with progressive sensory length-dependent polyneuropathy or autonomic dysfunction along with other symptoms, such as unexplained weight loss or arrhythmias, which should heighten suspicion for ATTR polyneuropathy. Family history of hereditary ATTR also plays a crucial role in these regions.[1]

In the non-endemic regions like the United States, idiopathic rapidly progressive sensory motor polyneuropathy or atypical chronic inflammatory demyelinating polyneuropathy should raise suspicion if accompanied by one or more red-flag symptoms.[1]

Typically, symptoms start in the distal lower extremities and progress proximally. Patients experience progressive sensory loss, balance issues, and difficulties with fine motor movements.[1,6,7] Unlike other polyneuropathies, hereditary ATTR with polyneuropathy tends to

progress much faster.[8]

Dr Caudle:
Thank you so much for that detailed background, Dr Brannagan. And now, Dr Urey, I'd like to shift our focus to ATTR cardiomyopathy. What are the red-flag symptoms or signs that should raise suspicion of ATTR amyloidosis?

Dr Urey:
So, in this case, clinicians should maintain a high index of suspicion in patients with heart failure with preserved ejection fraction who are worsening on guideline-directed medical therapy.[9,10]

Red flags for ATTR cardiomyopathy overlap in some areas with those for ATTR polyneuropathy and include preceding bilateral carpal tunnel syndrome, spinal stenosis, or biceps tendon rupture. That's why a detailed patient history is crucial to look for these and other red-flag symptoms, such as multisystem organ involvement, autonomic dysfunction, and, of course, unexplained peripheral neuropathy.[9,11]

Cardiac red flags include a discordance between ECG voltage and wall thickness seen on cardiac imaging, orthostatic hypotension, and intolerance to standard heart failure medications, such as ACE inhibitors and beta-blockers.[2,3,5]

It's also essential to maintain a high index of suspicion for ATTR cardiomyopathy in patients presenting with a constellation of non-cardiac symptoms, especially if they have a relevant medical history or comorbidities.[10,11]

Dr Caudle:
So then let's dive deeper into the clinical suspicion for ATTR cardiomyopathy. Staying with you, Dr Urey, how do experts recommend suspecting and diagnosing this?

Dr Urey:
Well, the current expert consensus recommendations emphasize a structured approach to a diagnosis, as outlined in the 2022 American Heart Association, American College of Cardiology, and Heart Failure Society of America guidelines for the management of heart failure. These guidelines establish screening criteria to facilitate the diagnosis of ATTR cardiomyopathy through non-invasive measures. The diagnostic process starts with a comprehensive evaluation that includes a thorough history, an ECG, and an echocardiogram.[12]

On an ECG, clinicians should look for discrepancies between QRS voltage and left ventricular wall thickness, conduction abnormalities such as atrioventricular block, and arrhythmias.[9,10]

Echocardiography can also reveal several key features, including biventricular hypertrophy, restrictive left ventricular filling, diastolic dysfunction, and reduced longitudinal strain with apical sparing.[9,10,13] One critical marker is left ventricular wall thickness of at least 12 millimeters or greater along with one or more red-flag symptom or specific clinical scenario identified by the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases.[5]

While not mandatory to make the diagnosis, cardiac magnetic imaging is another valuable tool. It can show myocardial amyloid infiltration, diffuse late gadolinium enhancement, or increased extracellular volume.[9,10,13] If these initial tests increase clinical suspicion, the next step is to differentiate ATTR amyloidosis from light chain amyloidosis.[9]

Differentiation starts with serum and urine immunofixation for monoclonal protein and serum free light chains. If the monoclonal protein screen is positive, patients should be referred to hematology-oncology and consider a cardiac or other biopsy to confirm amyloid deposition. If the monoclonal light chain screen is negative, however, the next step is bone scintigraphy or technetium-99m pyrophosphate scanning, which is a nuclear imaging test used to detect cardiac amyloid deposits.[9]

A positive technetium-99m pyrophosphate scan can only be interpreted in the context of a negative monoclonal light chain screen, as it can also be positive in light chain amyloidosis. And with a negative result, if there's high clinical suspicion, one may still proceed to biopsy.[9,12]

Once ATTR cardiomyopathy is suspected or confirmed, recommendations across guidelines and consensus documents direct that the next step is to perform transthyretin genotyping to distinguish between hereditary and wild-type forms. This step is essential for guiding further management and family counseling. Additionally, all guidelines, including those from the American College of Cardiology, recommend that patients with hereditary ATTR should be assessed for polyneuropathy symptoms to ensure comprehensive management of the condition.[12,14–16]

Dr Caudle:
Thank you. And as a follow-up to that last statement, Dr Brannagan, can you tell us more about how clinicians can assess polyneuropathy symptoms in all patients with hereditary ATTR?

Dr Brannagan:
Of course. So mixed phenotype, which presents with non-cardiac symptoms in addition to cardiac symptoms, is increasingly being recognized as a common clinical presentation across multiple gene variants of ATTR amyloidosis.[1,9,17–21] And so it's crucial for clinicians to assess patients with signs of ATTR cardiomyopathy for polyneuropathy symptoms to identify patients with a mixed phenotype. These include both autonomic and sensory polyneuropathy symptoms. Recognizing these early indicators can be key in diagnosing the full breadth of ATTR amyloidosis.[5,12,14,15]

Fortunately, the diagnosis of ATTR polyneuropathy can be made with simple assessment tools. First, clinicians should take a thorough medical history and conduct a review of systems. This includes assessing for autonomic dysfunction, such as gastrointestinal symptoms, syncope, and orthostatic hypotension. Nerve conduction studies are also valuable in confirming the diagnosis.[1,11,14,22]

In my own practice, we use the stages of familial amyloid polyneuropathy, or FAP score, as a guide to the progression of the disease. In addition, the Polyneuropathy Disability, or PND, score grades the impact of neuropathy on ambulation.[1,23]

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 Dr Thomas Brannagan and Dr Marcus Anthony Urey about diagnosing ATTR amyloidosis.

So, Dr Urey, in your clinical practice, what's been your approach to managing patients diagnosed with ATTR amyloidosis in the best-case scenario?

Dr Urey:
Well, in the best-case scenario, managing patients diagnosed with ATTR amyloidosis involves a comprehensive and coordinated approach by a multidisciplinary team.[24] The team typically includes neurologists, hematologists, cardiologists, nephrologists, gastroenterologists, clinical pharmacists, nurse specialists, nurse case managers, geneticists, and social workers.[24]

Ongoing collaboration with regular multidisciplinary meetings helps to coordinate patient care, identify appropriate research studies for disease-targeted interventions, manage symptoms, and optimize treatment plans.[24]

Dr Caudle:
Now obviously that was the best-case scenario, but what is more commonly the case for most healthcare providers, Dr Brannagan?

Dr Brannagan:
So unfortunately, diagnosing ATTR amyloidosis can be quite challenging for many healthcare providers due to limited resources and access to specialists.

One major challenge is the nonspecific nature of many ATTR amyloidosis symptoms, which can overlap with more common conditions, and this can lead to a delay in diagnosis and disease management.[1,2,10] There are ways we can address this, though. Healthcare providers, including cardiologists who are often seeing patients with symptoms of ATTR cardiomyopathy, can start by maintaining a high index of suspicion, especially when patients present with red-flag symptoms, such as bilateral carpal tunnel syndrome, lumbar spinal stenosis, biceps tendon rupture, or unexplained peripheral neuropathy.[9,11]

Fortunately, simple tools like thorough history taking, basic blood tests, and initial imaging studies can help identify patients who need further evaluation. And once a high suspicion is established, referral to specialized centers for confirmatory testing, such as bone scintigraphy or genetic testing, can be arranged.[1,3,6,11,12,14,22,25]

Dr Caudle:
Thank you for that. And now, unfortunately, we're almost out of time for today, but before we come to a close, Dr Brannagan, what key takeaways would you like to leave our audience today?

Dr Brannagan:
Well, I'd like to reiterate that once hereditary ATTR is suspected, genetic testing is crucial for identifying the specific type and guiding further management.[5,12,14,15] Also cascade genetic screening can be helpful to identify any family members at risk for disabling neuropathy and cardiomyopathy.[14]

The early assessment of polyneuropathy symptoms in hereditary ATTR patients is essential for improving outcomes.1 And by maintaining a high index of suspicion and then using simple assessment tools, we can expedite the diagnosis and improve patient care.[1]

Dr Caudle:
Well, thank you so much for sharing, Dr Brannagan. And how about you, Dr Urey? What final thoughts would you like to share?

Dr Urey:
I agree with Dr Brannagan that early detection and intervention is critical.[1] As a cardiologist, I often see patients with an ATTR cardiomyopathy phenotype. But we should recognize that concomitant polyneuropathy in a mixed phenotype is seen across multiple gene variants.[1,2] And so we need to keep a high index of suspicion to evaluate these patients thoroughly. One can consider collaborating with a neurologist to ensure that these patients get the appropriate diagnostic evaluation.[2]

Dr Caudle:
Thank you both, these are insightful takeaways from our discussion. And with those final thoughts in mind, I'd like to thank my guests, Drs Thomas Brannagan and Marcus Anthony Urey, for sharing their perspectives on diagnosing hereditary ATTR amyloidosis.

Dr Brannagan and Dr Urey, it was great speaking with you both today.

Dr Brannagan:
Well, it was great speaking with you both, also. Thank you.

Dr Urey:
Thank you.

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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