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Improving Outcomes in hATTR-PN: The Role of Vigilant Symptom Assessment

**Announcer:**
Welcome to ReachMD. This medical industry feature, titled "*Improving Outcomes in ATTRv-PN: The Role of Vigilant Symptom Assessment*" 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 our discussion today, focusing on hereditary transthyretin-mediated amyloidosis polyneuropathy, will be highlighting its progressing symptoms and diagnostic challenges and sharing strategies to improve patient identification and diagnosis. Joining me in our discussion is Dr. Thomas Brannagan.

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:**
Well, thank you for having me.

**Dr Caudle:**
Of course. Now for some background, amyloidosis caused by the transthyretin protein, known as ATTR, is a rare but serious condition that can have devastating effects throughout the body. And the hereditary form of ATTR amyloidosis is frequently associated with polyneuropathy.[1]

So based on that, Dr Brannagan, can you elaborate on the characteristics of hereditary ATTR amyloidosis polyneuropathy and the impact of this disease on patients?

**Dr Brannagan:**
Well of course. So, hereditary transthyretin-mediated amyloidosis polyneuropathy, which we'll be referring to as ATTRv polyneuropathy, is inherited in an autosomal dominant manner with variable penetrance.[2–7] It's described as a progressive, symmetric, length-dependent sensorimotor polyneuropathy.[4,8] This means that patients typically experience symptoms of numbness and pain starting in the feet which gradually moves proximally to the upper limbs with progressive sensory loss, eventually resulting in impairment in gait, balance, and hand movements.[1,4,8] And what's unique to this disease is that the neuropathy often involves autonomic dysfunction quite early in the disease.[9,10]

There's also a lot of variability in presentation, and so misdiagnosis is common, which often delays diagnosis by about three to four years, and many patients see multiple doctors before receiving an accurate diagnosis.[1,11–15] As a result of these disease characteristics, median survival from diagnosis ranges from five to 15 years, with cardiac involvement and multiple organ failure being significant contributors to mortality.[9,16,17] And so early diagnosis is critical because it gives us the chance to offer interventions that could not only improve quality of life, but also maximize the patient's function.[14,18,19]

**Dr Caudle:**
So with that being said, how does ATTRv polyneuropathy affect patients' daily lives, and why is understanding the stages of disease progression important?

**Dr Brannagan:**

So I'd like to emphasize here that ATTRv neuropathy produces severe symptoms and advances much faster than other neuropathies—such as diabetic neuropathy, Charcot-Marie-Tooth disease, or idiopathic neuropathy—causing some patients to become wheelchair bound or bedridden in less than a decade.[1,20] In addition, this severe stage puts patients at a risk of bedsores, muscle atrophy, deep vein thrombosis, infections, and ultimately, death.[21]

Now, when it comes to assessing the progression of neuropathy in ATTR amyloidosis, there are two common scores. The first is the Polyneuropathy Disability, or PND, score which grades the impact of neuropathy symptoms on ambulation and has the following breakdown[1,16,22]

- PND I includes sensory disturbances but with preserved walking capacity.
- Patients with PND II have difficulty walking but don't need a cane yet.
- And PND IIIa, a cane is required, and in PND IIIb, two canes or a walker are required for walking
- And finally, patients in PND IV are confined to a wheelchair or are bed-bound.

The other method used to classify neuropathy in ATTR is the Familial Amyloid Polyneuropathy score, or the FAP stage, which describes the progression of disease as follows:[1,22]

- In Stage 1, the disease is limited to the lower limbs with slight weakness in the extensors of the big toes.
- In Stage 2, there is progression of motor signs where the patient needs to walk with the assistance of a cane or walker.
- And then in Stage 3, the patient uses a wheelchair or is bed-bound, experiencing generalized weakness and loss of reflexes.

The duration of each stage can vary based on the specific ATTR pathogenic variant involved, and early-onset disease tends to be less severe with a longer survival time.[16]

**Dr Caudle:**
So what additional symptoms and complications beyond sensorimotor manifestations may patients experience?

**Dr Brannagan:**
Patients with ATTRv amyloidosis often experience symptoms related to autonomic neuropathy, which occurs in about 50 to 80 percent of patients.[21] These symptoms can be an early clinical presentation and often include gastrointestinal issues like constipation or diarrhea, which may alternate, early satiety and unintentional weight loss.[9,21,23] Autonomic dysfunction can also present as cardiovascular issues like orthostatic hypotension and arrhythmias,[23] or genitourinary symptoms, such as erectile dysfunction, urinary incontinence, or nocturia.[21,23]

**Dr Caudle:**
For those just tuning in, you're listening to ReachMD. I'm Dr Jennifer Caudle, and today I'm speaking with Dr Thomas Brannagan about hereditary ATTR amyloidosis polyneuropathy.

Now if we turn our attention to diagnosis, Dr Brannagan, what are some of the challenges in diagnosing ATTRv polyneuropathy, and what factors may complicate its diagnosis?

**Dr Brannagan:**
Well, diagnosing ATTRv polyneuropathy can be challenging because its symptoms often mimic those of other neuropathies, making it difficult to distinguish from more common conditions.[4,8,23,24]

Additionally, the clinical phenotype is influenced by genetic, epigenetic, geographic, and environmental factors.[4,8] In fact, up to 77 percent of patients in non-endemic areas have no documented family history of the disease.[1] And because the disease has variable penetrance, symptoms can vary considerably, even among individuals with the same variant. So an individual who has a pathogenic variant may not even express amyloidosis symptoms at the time that they're seen, which can lead to diagnostic difficulties as well.[4,5,8]

Now our diagnostic approach begins with a comprehensive neurologic evaluation, including an assessment of sensory symptoms, motor loss, and autonomic dysfunction, a thorough physical examination, and electrodiagnostic tests like EMG and nerve conduction studies. Genetic testing is essential for an accurate diagnosis. And biopsy and amyloid typing are helpful to further characterize the disease.[1,25–27]

**Dr Caudle:**
Now since there seems to be a wide variety of non-specific signs, what red-flag symptoms should prompt consideration of ATTRv

polyneuropathy in patients?

**Dr Brannagan:**
Well, I'm glad you asked about this because identifying red-flag symptoms is crucial for suspecting ATTRv polyneuropathy.

These key symptoms include:

- Bilateral carpal tunnel syndrome—which is often an early indicator, as about 50 percent of patients diagnosed with ATTR previously had carpal tunnel syndrome[12,18,28–30]
- Lumbar stenosis[18,29–31]
- Dysautonomia—with symptoms such as alternating diarrhea and constipation and orthostatic hypotension[9,21,23,29,30]
- And cardiovascular signs like discordance between EKG voltage and wall thickness, intolerance to standard heart failure medications, and paradoxical low flow or low gradient aortic stenosis.[18,29,30]

In terms of considerations for correct diagnosis, there are several important points:

- Persistent symptoms despite carpal tunnel release or spinal surgery, or rapid progression in the severity of symptoms should raise suspicion for ATTRv polyneuropathy.[1,28,31]
- Patients who've been diagnosed with CIDP or an atypical inflammatory demyelinating polyneuropathy should also be evaluated for ATTRv polyneuropathy.[1]
- And recognizing these red-flag symptoms and considering them in the differential diagnosis may lead to earlier detection and timely management of ATTRv polyneuropathy.[1]

**Dr Caudle:**
So given everything we've talked about today, Dr Brannagan, do you have any final thoughts on how healthcare providers can improve the diagnosis and management of ATTRv polyneuropathy, especially considering its varied clinical presentation and potential for misdiagnosis?

**Dr Brannagan:**
Yeah, so improving the diagnosis of ATTRv polyneuropathy starts with recognizing its varied and often non-specific clinical presentation. Healthcare providers should maintain a high index of suspicion and consider ATTRv polyneuropathy in patients with a constellation of seemingly unrelated or unexplained symptoms. For example, a patient presents with orthostatic hypotension, gastrointestinal symptoms, and a history of carpal tunnel syndrome, these should collectively raise clinical suspicion for ATTRv polyneuropathy.[1,4,8,18,23,29,30]

So, let's talk about some actionable steps: It's first important to educate ourselves in recognizing the varied clinical presentation. We need to understand that ATTRv polyneuropathy includes *both* peripheral and autonomic symptoms, ranging from orthostatic hypotension and gastrointestinal issues to arrhythmias and cachexia.[1,15,18,26,32,33] As per consensus recommendations, we can assess patients through a detailed history and exam.[1]

In non-endemic areas like the United States, patients with an idiopathic rapidly-progressive sensorimotor axonal neuropathy or symptoms of an atypical inflammatory demyelinating polyneuropathy plus the presence of red-flag symptoms should raise our clinical suspicion for ATTRv amyloidosis.[1] In these patients, we should gather a detailed history and specifically enquire about family history, bilateral carpal tunnel syndrome, dysautonomia, or unexplained weight loss of at least five kilograms.[1] And during the clinical visit, we should then perform a detailed physical examination to evaluate for gait disorders, arrhythmias, or vitreous opacities. Further studies should also be conducted to evaluate for cardiac hypertrophy or nephropathy.[1]

Now, to make the diagnosis, after diagnosing the sensorimotor polyneuropathy with history, physical examination, and EMG/nerve conduction studies, the expert consensus panel recommends confirmation with DNA sequencing to confirm a diagnosis of ATTRv amyloidosis and to help identify pathogenic variants. Other helpful tests include a biopsy to test for amyloid deposition and amyloid typing.[1,25–27] With all of these in mind, I'd like to reiterate that proactively identifying ATTRv polyneuropathy is crucial due to the rapid progression of this fatal disease. Patients can experience reduced ambulation, impaired daily function, and a poor overall quality of life.[1,16,22] However, with early diagnosis and the opportunity for early intervention, we can aim to maximize patient function and quality of life.[14,18,19] And so by keeping these strategies in mind and staying alert to the varied presentation of ATTRv polyneuropathy, healthcare providers can improve the timely diagnosis and management of this condition. Because at the end of the day, it's all about

piecing together the puzzle and taking decisive steps to ensure patients receive the care that they need.

**Dr Caudle:**
Well, you've certainly given us a lot to think on as we come to the end of today's program.

I'd like to thank my guest, Dr Thomas Brannagan, for helping us better understand hereditary ATTR amyloidosis polyneuropathy and for sharing his insights on improving the diagnosis of this challenging condition.

Dr Brannagan, it was great speaking with you today.

**Dr Brannagan:**
Well, it was great to speak to you as well, Dr. Caudle. 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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