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Unraveling Hereditary ATTR Amyloidosis: Key Variants and Clinical Insights

Announcer:
Welcome to ReachMD. This medical industry feature, titled "Unraveling Hereditary ATTR Amyloidosis: Key Variants and Clinical Insights," 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 common variants and clinical presentations of hereditary transthyretin-mediated amyloidosis, also known as ATTR amyloidosis, are Drs Thomas Brannagan and Nitasha Sarswat. 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.

Dr Caudle:
Of course. And also with us is Dr Sarswat, Assistant Professor of Medicine in the Section of Cardiology, as well as the Director of the Infiltrative Cardiomyopathy program, at the University of Chicago. Dr. Sarswat, thank you so much for joining us today.

Dr Sarswat:
Great to be here.

Dr Caudle:
So, let's start our discussion with you, Dr Brannagan. Can you explain the key differences between hereditary ATTR amyloidosis and wild-type ATTR amyloidosis?

Dr Brannagan:
So hereditary ATTR amyloidosis and wild-type ATTR amyloidosis are essentially the same disease but with different mechanisms.[1–4]

Hereditary ATTR is caused by mutations in the TTR gene, leading to destabilization and dissociation of TTR tetramers, which then misfold and form amyloid fibrils.[1–4] It typically presents in the third to fifth decade of life and can manifest in three phenotypes with:[5,6]

- A: a predominantly polyneuropathy symptoms that are sensorimotor and autonomic,
- B: predominantly cardiomyopathy symptoms including heart failure,
- Or C: a mixed phenotype in which both polyneuropathy and cardiomyopathy symptoms are present.[7]

In comparison, wild-type ATTR is caused by a poorly understood age-related mechanism that results in instability and misfolding of the TTR protein.[1–4] It typically occurs in individuals over 60 years old. Wild-type ATTR primarily affects the heart but can also involve other organs and systems.[5,8,9] In fact, carpal tunnel syndrome is a common feature of both ATTR types.[4,10–12]

And we have data from a prospective study of 108 patients who underwent right heart catheterization and endomyocardial biopsy which found that 10 percent of patients with heart failure with preserved ejection fraction had either hereditary or wild-type ATTR.[13]

In a retrospective analysis of about 1500 patients, two out of five patients with ATTR were found to have the hereditary disease.[14]

Now, in the United States, patients with hereditary ATTR, approximately 60 percent have a mixed phenotype. So although each TTR gene variant is associated with a predominant phenotype, the majority of patients will actually exhibit multisystem involvement.[14]

Lastly, hereditary ATTR amyloidosis is transmitted in an autosomal dominant manner, meaning there's a 50 percent chance of an affected individual passing the pathogenic variant to their children.[6,15,16] However, the penetrance of the gene can vary, with some carriers remaining asymptomatic while others develop symptoms.[6,17] This variability in symptom expression, even among individuals with the same pathogenic variant, contributes to the disease's clinical heterogeneity.[6,17,18] The factors influencing the expression of symptoms are still unknown, but they likely involve a complex interplay of genetic, environmental, and possibly epigenetic factors.[6,18,19]

Dr Caudle:
Thank you so much for that breakdown, Dr Brannagan. And now if we turn to you, Dr Sarswat, what are the most common variants of hereditary ATTR amyloidosis?

Dr Sarswat:
Well, 47 different TTR variant have been reported in the US And this is based on the THAOS Registry, which is a global observational survey in individuals with hereditary or wild-type ATTR or who are asymptomatic carriers.[15]

The three most common variants in the US are V122I at about 45 percent, T60A at 20 percent, and V30M at six percent.[15]

I do want to note that there was a recent change to the naming convention. For example, V122I, which is isoleucine replacing valine at the 122nd amino acid position, is p.V142I with the new nomenclature. Both names refer to the same variant, but many of us still refer to it as V122I, as we'll do for this program.[20]

Now in terms of their clinical presentation, the V30M variant is primarily associated with polyneuropathy, but many patients also present with a cardiomyopathy at diagnosis. On the other hand, the T60A and the V122I variants are predominantly associated with cardiomyopathy, but neurologic involvement has also been noted at diagnosis.[6,21]

In fact, globally, up to 60 to 80 percent of patients with hereditary ATTR have a mixed phenotype, depending on the variant.[18,21–25]

This underscores the complexity of managing this condition because even within the same family, signs and symptoms of the disease can vary widely.[6,17,25]

So it's important to obtain a thorough history and exam to assess for both polyneuropathy and cardiomyopathy when suspecting ATTR disease and to collaborate closely with a neurologist to diagnose and manage the patient. And the key here is to send for a DNA sequencing in addition to amyloid typing and biopsy to confirm the hereditary ATTR diagnosis.[26–29]

And once hereditary ATTR is suspected or confirmed, genetic counseling and cascade genetic screening can be helpful to identify any family members at risk for disabling neuropathy and cardiomyopathy.[27]

Dr Caudle:
So then let's do an in-depth examination of these variants' clinical presentations, starting with V30M. Dr Brannagan, what key characteristics define this particular phenotype?

Dr Brannagan:
So globally, the V30M variant is the most common pathogenic variant responsible for polyneuropathy due to hereditary ATTR, but as I mentioned earlier, about 40 percent can present with cardiomyopathy.[6,21,25,30]

In non-endemic areas such as the United States, the V30M variant is associated with a positive family history in only 48 percent of cases. Here, patients with V30M typically present with late-onset disease at age 50 or older and exhibit primarily sensorimotor symptoms with relatively mild autonomic neuropathy.[4,25]

Dr Caudle:
Now let's turn to the V122I variant, which we noted is the most common pathogenic variant found in the US. Dr Sarswat, could you elaborate on its distinct clinical presentation and key characteristics?

Dr Sarswat:
Yes, so the V122I variant, now known as p.V142I, is the most common cause of hereditary ATTR in North America and it's predominantly found among individuals of African descent. In the US, the prevalence of the V122I variant is estimated to be around 3 to 4 percent, or about 1.5 million people, among the Black population.[31,32]

Carriers of the V122I variant mostly develop cardiomyopathy, but there is a significant presence of mixed phenotype, with both cardiac and neurologic symptoms.[33]

An epidemiological study of about 20,000 patients in the US and Canada found that approximately 71 percent of individuals who had hereditary ATTR had the V122I variant.[33]

Among these individuals, about 80 percent were Black, 60 percent were male, and the mean age was 69 years. Clinical manifestations included heart disease in about 80 percent of the patients and sensory or motor neuropathy in about 25 percent. And these clinical characteristics were similar between Black and White patients who had the V122I variant.[33]

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 and Dr Nitasha Sarswat about common variants in hereditary ATTR amyloidosis.

Now Dr Sarswat just noted that although it's typically linked with cardiomyopathy, the V122I variant is associated with neuropathic symptoms in over a quarter of patients with this pathogenic variant. So if we come back to you, Dr Brannagan, could you expand on this mixed-phenotype presentation?

Dr Brannagan:
Certainly. So, patients with the V122I variant, which again is classically considered to be a cardiomyopathy-dominant, often present with a mixed phenotype, including both cardiac and neurologic symptoms.[15,21,34]

From the THAOS Registry mentioned earlier, we've seen that around one-third of symptomatic patients with V122I variant report neuropathic pain, numbness, or tingling.[21]

And a similar proportion of mixed phenotype patients were seen in with V122I variant in a small study at the Mayo Clinic, where 30 percent of those patients had peripheral neuropathy and almost 20 percent had autonomic neuropathy at diagnosis.[15]

Dr Caudle:
And the final variant to discuss today is T60A, which is the second most common in the US. So, Dr Sarswat, do patients with this pathogenic variant, typically associated with a cardiomyopathy-dominant phenotype, also often present with neuropathy?

Dr Sarswat:
Yes, they often do present with the mixed phenotype we've discussed. In fact, a prospective study in the UK and Canada of patients with hereditary ATTR and the T60A variant showed that three-quarters had autonomic neuropathy and just over half had peripheral neuropathy at diagnosis. And so despite being considered cardiomyopathy-dominant, the T60A variant is also associated with a significant burden of neuropathy.[35]

Dr Caudle:
And as we come to a close, Dr Brannagan, what final thoughts would you like to leave with our audience today?

Dr Brannagan:
Well, I'd just like to emphasize that the three most common variants in the United States—which are V30M, T60A, and V122I, now also known as V50M, T80A, and p.V142I, respectively—all present with mixed phenotypes involving both cardiac and neurologic symptoms. And even pathogenic variants that are traditionally associated with cardiomyopathy often show significant neuropathy as well.[15,25]

This really highlights the need for a comprehensive neurological assessment in patients with hereditary ATTR amyloidosis, even for those with variants we typically think of as primarily affecting the heart.[26–29]

So because recognizing the early signs of ATTR polyneuropathy is crucial for timely diagnosis and management, a high index of suspicion and understanding of mixed phenotypes can significantly expedite the diagnosis.[7,25]

Dr Caudle:
Well, thank you, Dr Brannagan. And Dr Sarswat, I'll give you the final word.

Dr Sarswat:
To add to what Dr Brannagan just said, I'd like to highlight the role of genetic, environmental, and epigenetic factors in the clinical heterogeneity of hereditary ATTR amyloidosis. These factors also contribute to the varied clinical presentations we see.[6,19] So, I think it's crucial that we, as cardiologists, are familiar with the diverse presentations and work closely together with neurologists to diagnose and manage patients with hereditary ATTR amyloidosis.

Because at the end of the day, like Dr Brannagan stated, understanding this complexity helps us provide better care for our patients.

Dr Caudle:
Well thank you both for such an insightful discussion on the different variants of hereditary ATTR amyloidosis and their clinical presentation, as this conversation has certainly shed light on the complexities of the underrecognized mixed phenotypes. We appreciate your time and expertise, Dr Thomas Brannagan and Dr Nitasha Sarswat.

It was great speaking with you both today.

Dr Brannagan:
Well, thank you. And it was great speaking with you, too, Dr Caudle and Dr Sarswat.

Dr Sarswat:
You as well.

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.

References:

1. Hou X, Aguilar MI, Small DH. Transthyretin and familial amyloidotic polyneuropathy. *FEBS J*. 2007;274:1637-1650.
2. Bulawa CE, Connelly S, Devit M, et al. Tafamidis, a potent and selective transthyretin kinetic stabilizer that inhibits the amyloid cascade. *Proc Natl Acad Sci USA*. 2012;109:9629-9634.
3. Saraiva MJ. Transthyretin amyloidosis: a tale of weak interactions. *FEBS Lett*. 2001;498:201-203.
4. Sekijima Y. Transthyretin (ATTR) amyloidosis: clinical spectrum, molecular pathogenesis and disease-modifying treatments. *J Neurol Neurosurg Psychiatry*. 2015;86:1036-1043.
5. Coelho T, Ericzon BG, Falk R, et al. A guide to transthyretin amyloidosis. Published online 2018. Accessed November 8, 2024. https://amyloidosis.org/sites/default/files/pdf-docs/pages/resources/2023-03/2018%20ATTR.pdf
6. Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. *Orphanet J Rare Dis*. 2013;8:31.
7. Nativi-Nicolau JN, Karam C, Khella S, Maurer MS. Screening for ATTR amyloidosis in the clinic: overlapping disorders, misdiagnosis, and multiorgan awareness. *Heart Fail Rev*. 2022;27:785-793.
8. Brunjes DL, Castano A, Clemons A, Rubin J, Maurer MS. Transthyretin cardiac amyloidosis in older Americans. *J Card Fail*. 2016;22:996-1003.
9. Connors LH, Sam F, Skinner M, et al. Heart failure resulting from age-related cardiac amyloid disease associated with wild-type transthyretin: a prospective, observational cohort study. *Circulation*. 2016;133:282-290.
10. Karam C, Dimitrova D, Christ M, Heitner SB. Carpal tunnel syndrome and associated symptoms as first manifestation of hATTR amyloidosis. *Neurol Clin Pract*. 2019;9:309-313.
11. Nakagawa M, Sekijima Y, Yazaki M, et al. Carpal tunnel syndrome: a common initial symptom of systemic wild-type ATTR (ATTRwt) amyloidosis. *Amyloid*. 2016;23:58-63.
12. Kapoor M, Rossor AM, Laura M, Reilly MM. Clinical presentation, diagnosis and treatment of TTR amyloidosis.*J Neuromuscul Dis*. 2019;6:189-199.
13. Hahn VS, Yanek LR, Vaishnav J, et al. Endomyocardial biopsy characterization of heart failure with preserved ejection fraction and prevalence of cardiac amyloidosis. *JACC Heart Fail*. 2020;8:712-724.
14. Bazell C, Alston M, Kumar N, et al. Descriptive characteristics of patients diagnosed with transthyretin amyloidosis (ATTR) in the Medicare fee-for-service and commercial populations [poster]. Presented at: XIX Meeting of the International Symposium of Amyloidosis (ISA); May 26-30, 2024; Rochester, MN. Poster 518.
15. Maurer MS, Hanna M, Grogan M, et al. Genotype and phenotype of transthyretin cardiac amyloidosis: THAOS (Transthyretin Amyloid Outcome Survey). *J Am Coll Cardiol*. 2016;68:161-172.
16. Amyloidosis Foundation. Amyloidosis information: a general overview. Published online 2020. Accessed November 8, 2024. https://www.amyloidosis.org/sites/default/files/pdf-docs/pages/resources/2022-12/2020-patient-overview.pdf
17. Conceição I, Damy T, Romero M, et al. Early diagnosis of ATTR amyloidosis through targeted follow-up of identified carriers of TTR gene mutations. *Amyloid*. 2019;26:3-9.
18. Planté-Bordeneuve V, Said G. Familial amyloid polyneuropathy. *Lancet Neurol*. 2011;10:1086-1097.
19. Conceição I, González-Duarte A, Obici L, et al. "Red-flag" symptom clusters in transthyretin familial amyloid polyneuropathy. *J Peripher Nerv Sys*. 2016;21:5-9.

20. National Center for Biotechnology Information. ClinVar:p.Val142Ile. NIH. Accessed November 8, 2024. https://www.ncbi.nlm.nih.gov/clinvar/variation/13426/
21. Swiecicki PL, Zhen DB, Mauermann ML, et al. Hereditary ATTR amyloidosis: a single-institution experience with 266 patients. *Amyloid*. 2015;22:123-131.
22. Zampino S, Sheikh FH, Vaishnav J, et al. Phenotypes associated with the Val122Ile, Leu58His, and late-onset Val30Met variants in patients with hereditary transthyretin amyloidosis. *Neurology*. 2023;100:e2036-e2044.
23. Gentile L, Diemberger I, Plante-Bordeneuve V, et al. Phenotypic characteristics of F64L, I68L, I107V, and S77Y ATTRv genotypes from the Transthyretin Amyloidosis Outcomes survey (THAOS). *PLoS One*. 2024;19:e0292435.
24. Grogan M, Hawkins PN, Kristen A V, et al. Identifying mixed phenotype: evaluating the presence of polyneuropathy in patients with hereditary transthyretin-mediated amyloidosis with cardiomyopathy. *J Card Fail*. 2019;25:S9-S10.
25. Adams D, Ando Y, Beirão JM, et al. Expert consensus recommendations to improve diagnosis of ATTR amyloidosis with polyneuropathy. *J Neurol*. 2021;268:2109-2122.
26. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *J Am Coll Cardiol*. 2022;79:e263-e421.
27. Kittleson MM, Ruberg FL, Ambardekar AV, et al; Writing Committee. 2023 ACC expert consensus decision pathway on comprehensive multidisciplinary care for the patient with cardiac amyloidosis: a report of the American College of Cardiology solution set oversight committee. *J Am Coll Cardiol*. 2023;81:1076-1126.
28. Garcia-Pavia P, Rapezzi C, Adler Y, et al. Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC working group on myocardial and pericardial diseases. *Eur Heart J*. 2021;42:1554-1568.
29. Brito D, Albrecht FC, de Arenaza DP, et al. World Heart Federation Consensus on transthyretin amyloidosis cardiomyopathy (ATTR-CM). *Glob Heart*. 2023;18:59.
30. Hawkins PN, Ando Y, Dispenzeri A, Gonzalez-Duarte A, Adams D, Suhr OB. Evolving landscape in the management of transthyretin amyloidosis. *Ann Med*. 2015;47:625-638.
31. Chandrashekar P, Alhuneafat L, Mannello M, et al. Prevalence and outcomes of p.Val142Ile TTR amyloidosis cardiomyopathy: a systematic review. *Circ Genom Precis Med*. 2021;14:e003356.
32. United States® Census Bureau. QuickFacts: United States. Accessed November 8, 2024. https://www.census.gov/quickfacts/
33. Trachtenberg BH, Shah SK, Nussbaum RL, Bristow SL, Malladi R, Vatta M. Presence of V122I variant of hereditary transthyretin-mediated amyloidosis among self-reported White individuals in a sponsored genetic testing program. *Circ Genom Precis Med*. 2021;14:e003466.
34. Khella S, Polydefkis M, Drachman B, et al. Neurologic involvement in V122I familial amyloidosis [abstract]. Presented at: 63rd American Association of Neuromuscular & Electrodiagnostic Medicine 2016 Annual Meeting; September 14-17, 2016; New Orleans, LA. Abs 165.
35. Sattianayagam P, Hahn A, Whelan C, et al. Cardiac phenotype and clinical outcome of familial amyloid polyneuropathy associated with transthyretin alanine 60 variant. *Eur Heart J*. 2012;33:1120-1127.