NeuroNet pro

Hereditary Transthyretin-Mediated Amyloidosis (hATTR) Best Practices

Guide for Patient Identification and Diagnosis in Neurology Clinical Settings

Alnylam Pharmaceuticals proudly sponsors NeuroNet's Hereditary Transthyretin-Mediated Amyloidosis (hATTR) Best Practices.

OVERVIEW

This document is intended to serve as a quick reference guide to support the care of patients with hereditary transthyretin-mediated amyloidosis (hATTR).

ETIOLOGY

hATTR is a progressive, rare, inherited, multisystemic condition caused by variants in the transthyretin (TTR) gene.[1] The TTR gene encodes the transthyretin protein produced primarily by the liver. The variants cause dissociation of transthyretin protein, which leads to misfolding and formation of abnormal protein, amyloid.[1] Accumulation of amyloid occurs throughout the body's organs and tissues, especially affecting the nervous system and heart.[1]

GENETICS AND GEOGRAPHIC DISTRIBUTION

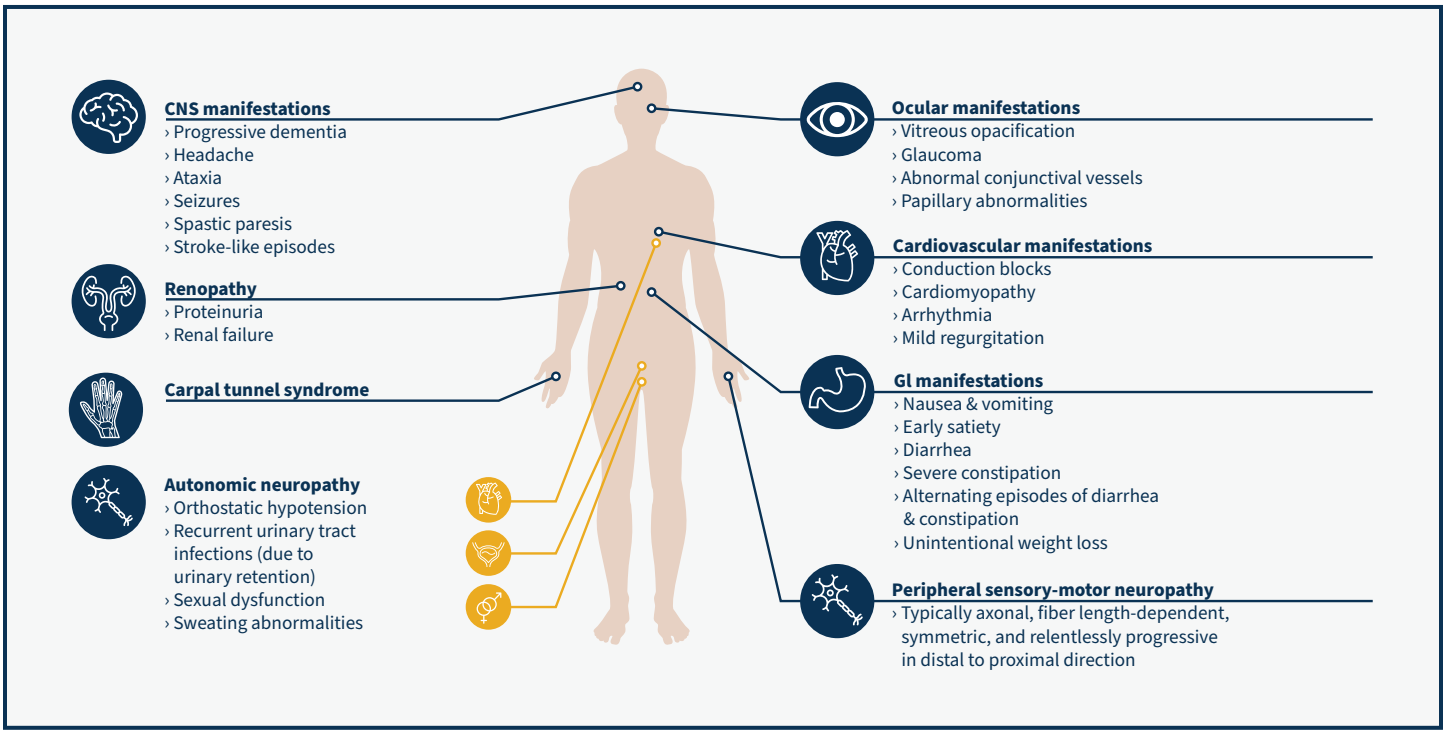
Over 140 pathogenic variants associated with hATTR have been identified worldwide.[1] Due to the autosomal dominant pattern of inheritance, hATTR tends to cluster in certain geographic regions or ethnic groups. As of 2019, hATTR had been documented in at least 29 countries throughout the world.[2] Originally, hATTR was identified in 3 main endemic locations in Portugal, Japan, and Sweden, with smaller clusters in Cyprus and Majorca.[2] Incidence throughout Europe and other nonendemic areas is sporadic, but increased incidence is projected due to improved diagnostic tools, such as genetic testing, and increased awareness of the condition. In the United States, the Transthyretin Amyloidosis Outcomes Survey (THAOS) registry reported over 30 different pathogenic TTR variants, the most common being Val122Ile (45%), Thr60Ala (20%), and Val30Met (6%).[3] The V122I variant is reported in 3% to 4% of Black Americans.[4,5]

CLINICAL PRESENTATION

As there are no specific signs or symptoms of polyneuropathy that are unique to hATTR, its occurrence should be considered in the context of additional red flags, including neuropathy (nerve damage that can cause loss of sensation) on one or both sides of the body, paired with at least one of the following symptoms[1,6]:

- Carpal tunnel syndrome in both wrists
- Lumbar spinal stenosis
- Tendon rupture
- Dry mouth, erectile dysfunction, orthostatic hypotension, and other signs of autonomic dysfunction
- Fatigue or other symptoms of heart failure
- Severe diarrhea or constipation
- Incontinence and increased urinary frequency
- Unexplained weight loss
- Blurred vision and dry eyes

Additional clinical features and manifestations of hATTR are shown in **Figure 1**.



CNS, central nervous system; GI, gastrointestinal.

Figure 1: Clinical features and manifestations of hATTR.[6]

Adapted from Conceição I, Gonzalez-Duarte A, Obici L, et al. "Red-flag" symptom clusters in transthyretin familial amyloid polyneuropathy. *J Peripher Nerv Syst*. 2016;21(1):5-9.

Clinical phenotype appears to be related to the specific TTR variant. Some variants (such as Val122Ile, Ile68Leu, Thr60Ala, and Leu111Met) manifest with cardiomyopathy as the predominant feature, while others (such as Ala97Ser and Ser50Arg) present more often with a neurological phenotype.[2]

The age at onset and geographical origin also influence the phenotype. Patients from endemic areas have traditionally been described as having an early-onset (age <50 years) or late-onset disease (age ≥50 years).[2]

The typical presentation of early onset includes involvement of small fibers, which is characteristic of the V30M hATTR phenotype, and progresses to the larger fibers (sensory and motor), leading to accumulation of disability and ultimately death.[2,6,7]

The presentation of late onset disease is more variable and includes sensory and motor neuropathy symptoms, bilateral carpal tunnel syndrome, and cardiac involvement.[2,6,7]

A prior history of renal failure with proteinuria, ophthalmologic vitreous opacities, or cardiac symptoms such as shortness of breath, arrhythmias, congestive heart failure with preserved ejection fraction, and hypertrophic cardiomyopathy should raise suspicion of hATTR.[6]

"The most striking feature of hATTR neuropathy in the differential diagnosis is its progressive course. On average, patients with the early-onset form progress from familial amyloid polyneuropathy (FAP)-1 to FAP-2 stage of disease in 5.6 years and from FAP-2 to FAP-3 in 4.8 years. In patients with the late-onset form, progression is even faster and requires 2 to 4 years for switching from FAP-1 to FAP-2 and 2 to 3 years from FAP-2 to FAP-3."[8]

BARRIERS TO AN ACCURATE DIAGNOSIS

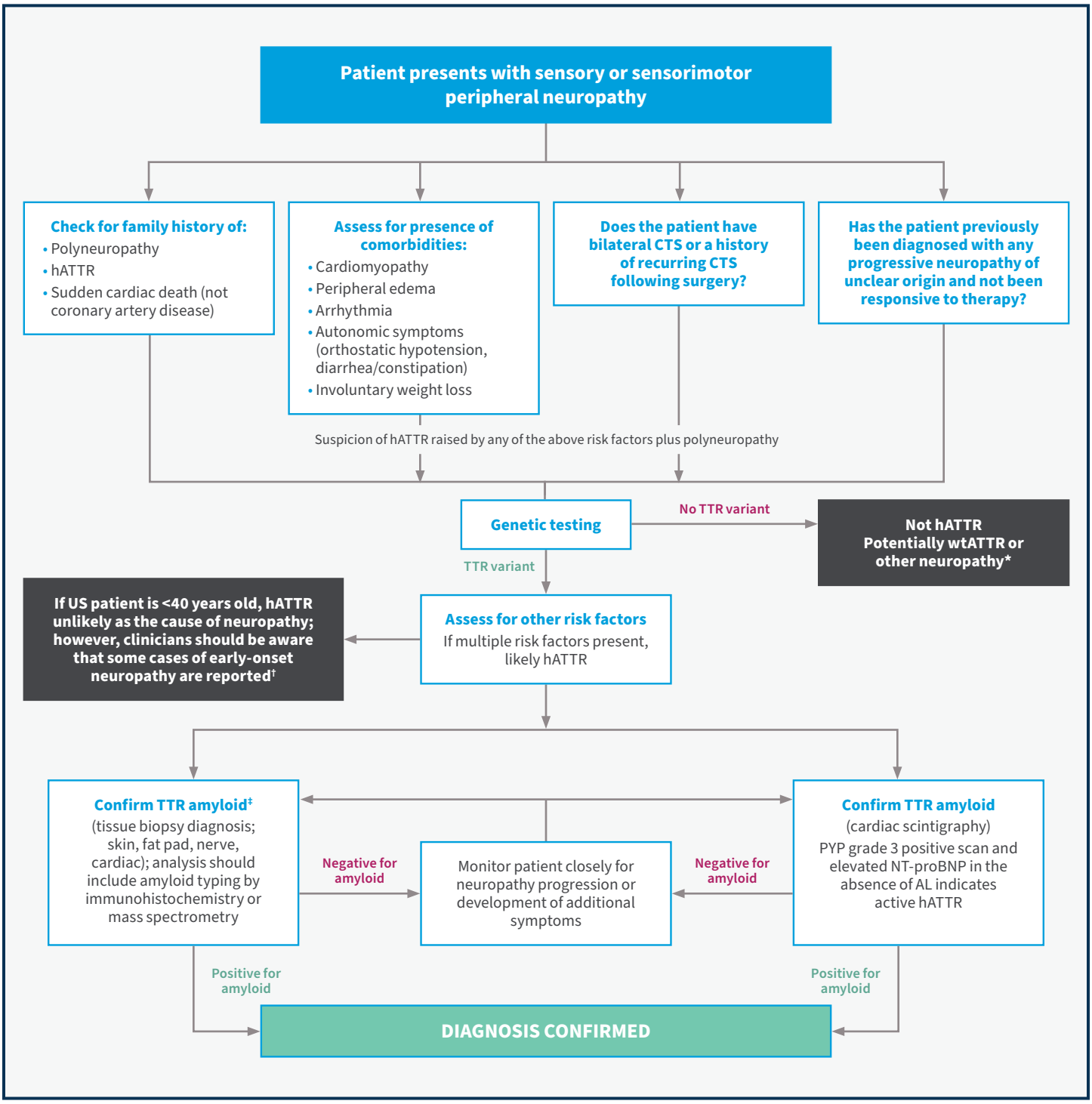
Endemic areas already have a high suspicion of the disease. After a variant has been identified, genetic testing and counseling of asymptomatic carriers is key. In nonendemic regions, a lack of suspicion tends to delay diagnosis for 3 to 4 years, usually without family history and clinical heterogeneity mimicking other peripheral neuropathies.[9] **Table 1** lists common misdiagnoses.

Neuropathy phenotype or manifestation	Common misdiagnoses	Factors informing decision to perform differential diagnostic assessment	Characteristics that may indicate hATTR
Length-dependent peripheral neuropathy	• Diabetic neuropathy • Idiopathic neuropathy • Alcohol neuropathy	• Mild diabetes with severe neuropathy • Weakness with sensory abnormalities; rapid progression • Concurrent development of other symptoms (erectile dysfunction, change in bowel habits); history of other conditions (eg, unexplained weight loss)	• Concurrent cardiac disease • Nerve biopsy findings • Early motor involvement • Previous or concurrent CTS • Concurrent cardiac history: CHF, arrhythmia, or syncope
Demyelinating neuropathy	• CIDP	• Primarily axonal polyneuropathy; no or poor response to prior immunotherapy; accompanying autonomic symptoms • Family history or other amyloid complication	
Motor neuropathy	• Motor neuron disease/ALS • CIDP	• Concurrent sensory component	• Other organ involvement • Prominent sensory symptoms distinguishes from ALS
Small-fiber neuropathy	• Fibromyalgia • Idiopathic small-fiber neuropathy	• Other associated features of hATTR amyloidosis • Small-fiber neuropathy rapidly progressing to mixed-fiber (small and large) neuropathy	• Other organ involvement; constellation of red-flag symptoms
Bilateral CTS	• Occupational CTS	• New-onset CTS despite no recent work history/history of repetitive motions • Presence of other complications (eg, HF)	• Concurrent idiopathic neuropathy or autonomic dysfunction • Trigger finger; lumbar stenosis • Recurrent CTS
Unexpected weight loss	• Malignancy or autoimmune disease	• Other associated features of hATTR	

ALS, amyotrophic lateral sclerosis; CHF, chronic heart failure; CIDP, chronic inflammatory demyelinating polyneuropathy; CTS, carpal tunnel syndrome; hATTR, hereditary transthyretin-mediated amyloidosis; HF, heart failure.

Table 1: Common misdiagnoses in patients with hATTR.[1]

CLINICAL WORKFLOW TO IMPROVE IDENTIFICATION OF hATTR (FIGURE 2)[1]



AL, amyloid light chain; CTS, carpal tunnel syndrome; hATTR, hereditary transthyretin-mediated amyloidosis; NT-proBNP, N-terminal pro-brain natriuretic peptide; PYP, pyrophosphate; TTR, transthyretin; US, United States; wtATTR, wild-type transthyretin-mediated amyloidosis.

*Patients may be assessed for genetic conditions including Charcot–Marie–Tooth disease and hereditary neuropathy with liability to pressure palsies, or screened for vitamin B12 deficiency, diabetes (hemoglobin A1C assessment), thyroid dysfunction, monoclonal gammopathy (immunofixation electrophoresis), or AL amyloidosis (immunoglobulin free light chain assessment).
†Early onset of polyneuropathy has been reported in hATTR amyloidosis.
‡Importance of tissue diagnosis is greater when concurrent possible causes of peripheral neuropathy (eg, B12 deficiency, diabetes mellitus, paraproteinemia) are present. In certain cases where there is no alternative cause for a progressive neuropathy, especially when multisystem features are present, a biopsy may not be necessary. A negative tissue biopsy in a patient with a high suspicion of hATTR does not exclude a diagnosis, and further investigation (ie, scintigraphy) or close follow-up is warranted.

Figure 2: Key considerations and recommended assessments for diagnosis of hATTR with polyneuropathy in the US.

Adapted from Karam C, Mauermann ML, Gonzalez-Duarte A, et al. Diagnosis and treatment of hereditary transthyretin amyloidosis with polyneuropathy in the United States: Recommendations from a panel of experts. *Muscle Nerve*. 2024;69(3):273-287.

GENETIC TESTING

One option for genetic testing to consider is no-charge testing through Alnylam Act®. To be eligible for genetic testing through Alnylam Act®, patients must be at least 18 years old, live in the US or Canada, and meet the requirements below:

- Family history of hATTR, *OR*
- Suspected diagnosis of hATTR

Fax the requisition form to (715) 406-4175 with the specimen collection kit or order via Alnylam.preventiongenetics.com.

Refer the patient for genetic counseling when you order a genetic test*:
You can select optional pretest and/or post-test genetic counseling when filling out the test requisition form. Genome Medical will contact the patient directly to schedule an appointment.

Prepare the patient for the appointment:
It is recommended that the patient set aside thirty minutes free from interruptions or distractions. The patient may consider asking family members about their family medical history ahead of the appointment. It is helpful for the genetic counselor to understand if any family members have been diagnosed with medical conditions and at what age they were diagnosed.

Receive the results†:
Genome Medical will email the patient a summary report, and patients may access the report through the online portal. The patient may then share the report results with you.

The Alnylam Act® program was created to provide access to genetic testing and counseling to patients as a way to help people make more informed decisions about their health.

- While Alnylam provides financial support for this program, tests and services are performed by independent third parties
- Healthcare professionals must confirm that patients meet certain criteria to use the program
- Alnylam receives de-identified patient data from this program, but at no time does Alnylam receive patient-identifiable information. Alnylam may use healthcare professional contact information for research purposes
- Both genetic testing and genetic counseling are available in the US and Canada
- Healthcare professionals or patients who use this program have no obligation to recommend, purchase, order, prescribe, promote, administer, use, or support any Alnylam product
- No patients, healthcare professionals, or payers, including government payers, are billed for this program

*Both genetic testing and genetic counseling are available in the US and Canada.
†If the test result is negative, Genome Medical will provide the patient with an educational video explaining the results.

For questions about genetic testing and counseling
Contact PreventionGenetics at preventiongenetics.com/contactUs or 715-387-0484.

CONSIDERATIONS TO IMPROVE hATTR IDENTIFICATION IN YOUR PRACTICE

Query your electronic health record (EHR) system to identify current patients with existing clinical red flags for hATTR. Note that EHR query functions may differ. Refer to your EHR's reporting or query guide.

Steps to query your EHR:

1. Log in to the EHR system. If needed, contact your administrator to ensure you have permission to access the reporting or query module.
2. Locate the reporting or query module in the EHR system. If you are unsure where this is or if access needs to be granted, contact your administrator or the EHR vendor's customer support for assistance.
3. If you have criteria to filter by (eg, age, gender, location), apply those first before filtering by diagnosis codes.
4. Enter the following list of diagnosis codes that may indicate early signs of hATTR.

Diagnosis	ICD-10 Code
Neuropathic heredofamilial amyloidosis; heredofamilial amyloidosis, unspecified	E85.1, E85.2
Polyneuropathies and other disorders of the peripheral nervous system	G60, G61, G62, G63, G64
Family history of ATTR	E85.1, E85.82, Z83.49
Coronary artery disease	I25.1, I25.119, I25.110
Congestive heart failure	I50.2, I50.4, 150.9
Peripheral edema	R60.9
Bilateral carpal tunnel syndrome	G56.0, G56.03
Other idiopathic peripheral autonomic neuropathy	G90.09
Orthostatic hypotension	I95.1
Syncope	R55
Disorder of the autonomic nervous system, unspecified	G90.9
Chronic diarrhea	K59.1, R19.7
Constipation	K59
Alternating diarrhea and constipation	K58.2, R19.4
Unexplained weight loss	R63.4
Sexual dysfunction	R37, F52.21, F52.22, F52.9, F66
Sweating abnormalities	R61
Recurrent urinary tract infections (UTIs)	Z87.440
Vitreous opacities	H43.399
Renal abnormalities	R93.429, R94.4, N28.9, Q63.9

ICD-10, International Classification of Diseases, Tenth Revision.

Steps to query your EHR (cont'd):

5. After applying the diagnosis code filter, apply any additional criteria needed to refine the query (eg, date range, physician name). Some EHR systems now use artificial intelligence (AI) technology to simplify this process, allowing you to apply all filters in a single step.
6. Run a preliminary query to ensure the data pull correctly, and review the initial results for any inconsistencies or errors. It is recommended to cross-check a sample of patients from the list to verify accuracy.
7. If needed, refine the query parameters to narrow or broaden the results based on the initial output.
8. Once you have your list of patients, distribute it to the treating physician to review the chart in more detail to consider if genetic testing for hATTR is appropriate.
9. Save the report for future querying and consider the cadence of generating frequency (eg, monthly/quarterly/semiannually).

EHR Triggers or Pop-ups: These EHR functions represent valuable tools for promoting awareness of clinical suspicion for hATTR, including genetic testing options, facilitating informed decision-making, and ultimately improving patient care—particularly in the context of hATTR, where early detection is key.

Family Testing: Genetic testing is essential for identifying at-risk relatives and enabling early detection and intervention. Understanding the genetic makeup of family members allows for personalized management strategies to manage disease progression effectively.

Nonspecific Symptoms: People with hATTR commonly present with nonspecific symptoms, which contribute to underdiagnosis and/or misdiagnosis. The key to diagnosis is a high index of suspicion, which can be maintained by continuing education for providers.

Clinical Assessment Phenotype With Genotype: To diagnose genetically diverse conditions, a multidisciplinary team involving geneticists, pathologists, physicians, and genetic counselors is crucial. While advanced techniques like next-generation sequencing aid in diagnosing genetic diseases, clinical examination remains essential to match clinical phenotype with genotype accurately.

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ADDITIONAL READING

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