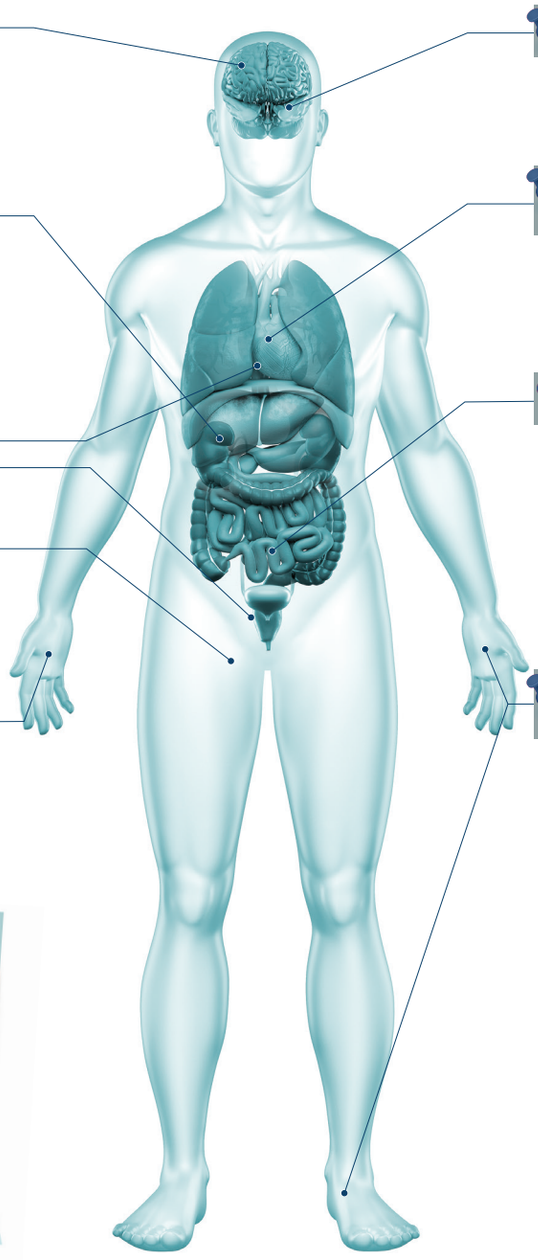
Hereditary ATTR amyloidosis:
a life-threatening, multisystem disease[1-4]

Hereditary ATTR (hATTR) amyloidosis is an inherited, rapidly progressive, life-threatening disease.[2,3,5] It is caused by a mutation in the transthyretin (*TTR*) gene that results in misfolded TTR proteins accumulating as amyloid fibrils in multiple sites including the nerves, heart, and GI tract.[2,6,7] Patients with hATTR amyloidosis can present with symptoms across a spectrum that includes:[1,3,4]

- Peripheral sensory-motor neuropathy
- Autonomic dysfunction
- Cardiomyopathy

Constellation of possible signs and symptoms of hATTR amyloidosis



CNS manifestations
- Progressive dementia
- Stroke-like episodes
- Ataxia

Nephropathy
- Proteinuria
- Renal failure

Autonomic neuropathy
- Orthostatic hypotension
- Recurrent urinary tract infections (due to urinary retention)
- Sexual dysfunction
- Sweating abnormalities

Carpal tunnel syndrome

Ocular manifestations
- Vitreous opacification
- Glaucoma

Cardiovascular manifestations
- Conduction block
- Cardiomyopathy
- Arrhythmia

GI manifestations
- Nausea and vomiting
- Early satiety
- Diarrhoea
- Severe constipation
- Alternating episodes of diarrhoea and constipation
- Unintentional weight loss

Peripheral sensory-motor neuropathy
- Neuropathic pain
- Altered sensation (i.e., change in sensitivity to pain and temperature)
- Numbness and tingling
- Muscle weakness
- Impaired balance
- Difficulty walking

Symptom presentation can be highly varied even among individuals in the same family. However, certain symptom clusters should raise suspicion of a single underlying condition[1, 8]

Adapted from Conceição I, et al. *J Peripher Nerv Syst.* 2016;21(1):5-9
ATTR, TTR amyloidosis; GI, gastrointestinal; hATTR, hereditary ATTR (hATTR) amyloidosis; TTR, transthyretin

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See the next page to learn how to **recognize the red-flag symptoms** of hATTR amyloidosis

Recognize the red-flag symptoms. **Suspect** hATTR amyloidosis.

Patients with hATTR amyloidosis require an early and accurate diagnosis due to the rapid natural progression of the disease[1,9,10]

The clinical manifestation of hATTR amyloidosis can vary widely, and recognizing the signs can be crucial to an early diagnosis[1]

The combination of peripheral neuropathy with autonomic dysfunction or cardiac involvement may indicate hATTR amyloidosis[1]

Progressive symmetric sensory-motor neuropathy and ≥1 of the following:

- Bilateral carpal tunnel syndrome
- Nephropathy (e.g., proteinuria or renal failure)
- Early autonomic dysfunction (e.g., erectile dysfunction or postural hypotension)
- Gastrointestinal complaints (e.g., chronic diarrhoea, constipation, or diarrhoea/constipation)
- Unexplained weight loss
- Cardiovascular manifestations (e.g., conduction block, cardiomyopathy, or arrhythmia)
- Vitreous opacities
- Positive family history

Additional signs: rapid disease progression or failure to respond to immunomodulatory treatment

Adapted from Conceição I, et al. *J Peripher Nerv Syst.* 2016;21(1):5-9

If hATTR amyloidosis is suspected, genetic testing can help confirm the diagnosis[8,10]

ATTR, TTR amyloidosis; hATTR, hereditary ATTR (hATTR) amyloidosis; TTR, transthyretin

References: 1. Conceição I, González-Duarte A, Obici L, et al. "Red-flag" symptom clusters in transthyretin familial amyloid polyneuropathy. *J Peripher Nerv Syst.* 2016;21(1):5-9; **2.** Hanna M. Novel drugs targeting transthyretin amyloidosis. *Curr Heart Fail Rep.* 2014;11(1):50-57; **3.** Mohty D, Damy T, Cosnay P, et al. Cardiac amyloidosis: updates in diagnosis and management. *Arch Cardiovasc Dis.* 2013;106(10):528-540; **4.** Shin SC, Robinson-Papp J. Amyloid neuropathies. *Mt Sinai J Med.* 2012;79(6):733-748; **5.** Adams D, Coelho T, Obici L, et al. Rapid progression of familial amyloidotic polyneuropathy: a multinational natural history study. *Neurology.* 2015;85(8):675-682; **6.** Damy T, Judge DP, Kristen AV, et al. Cardiac findings and events observed in an open-label clinical trial of tafamidis in patients with non-Val30Met and non-Val122Ile hereditary transthyretin amyloidosis. *J Cardiovasc Transl Res.* 2015;8(2):117-127; **7.** Hawkins PN, Ando Y, Dispenzeri A, et al. Evolving landscape in the management of transthyretin amyloidosis. *Ann Med.* 2015;47(8):625-638; **8.** Ando Y, Coelho T, Berk JL, et al. Guidelines of transthyretin-related hereditary amyloidosis for clinicians. *Orphanet J Rare Dis.* 2013;8:31; **9.** Adams D, Suhr OB, Hund E, et al. First European consensus for diagnosis, management, and treatment of transthyretin familial amyloid polyneuropathy. *Curr Opin Neurol.* 2016;29(Suppl 1):S14-S26; **10.** Obici L, Kuks JC, Buades J, et al. Recommendations for presymptomatic genetic testing and management of individuals at risk for hereditary transthyretin amyloidosis. *Curr Opin Neurol.* 2016;29(Suppl 1):S27-S35

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