ATTR Symptoms and Manifestations
Early indicators

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ATTR Disease State Slide Deck

- This resource provides information about ATTR.
- This resource is intended to be viewed in its entirety to support scientific exchange and is not intended as recommendations for clinical practice.
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Early Indicators of ATTR-CM

Importance of earlier detection

- A diverse spectrum of additional clinical manifestations must be considered when evaluating potential ATTR-CM[1]
  - Early indicators, that pre-exist cardiac disease development, of ATTR-CM include carpal tunnel syndrome, lumbar spinal stenosis, previous orthopedic procedures, and spontaneous biceps tendon rupture[1,2]

Early Indicator of ATTR-CM	Details
Carpal tunnel syndrome	CTS typically occurs 5-10 years prior to development of cardiac manifestations[3] • In hATTR-CM, CTS was the most frequently (85.3%) diagnosed musculoskeletal manifestation, with 47.1% of patients undergoing CTS release an average of 6.7 years prior to diagnosis[2] • High frequency of CTS in patients with wtATTR (35-53%)[2,4-6]
Lumbar spinal stenosis	On average, spinal stenosis laminectomy predates diagnosis of hATTR with cardiomyopathy and wtATTR amyloidosis with cardiomyopathy by 4.0 and 6.3 years, respectively[2]
Rotator cuff tear	Rotator cuff repair can predate the diagnosis of wtATTR-CM by 7.4-10.3 years[2]
Total hip and knee arthroplasties	On average, arthroplasty occurs 7.0-8.9 years before ATTR diagnosis[2,7]

ATTR, transthyretin amyloidosis; hATTR, hereditary ATTR with cardiomyopathy; wtATTR, wild-type with cardiomyopathy; CTS, carpal tunnel syndrome.

1. Mauer et al. *Circ Heart Fail.* 2019;12(9):e006075; 2. Campbell et al. *ISA Congress.* 2020. Poster PT119; 3. Sperry et al. *J Am Coll Cardiol.* 2018;72:2040–50; 4. Sekijima et al. *Amyloid.* 2018;25:8–10; 5. Fosbol et al. *J Am Coll Cardiol.* 2019;74:15–23; 6. Maurer et al. *J Am Coll Cardiol.* 2016;68:161–72. 7. Rubin et al. *Amyloid.* 2017;24(4):226–30.

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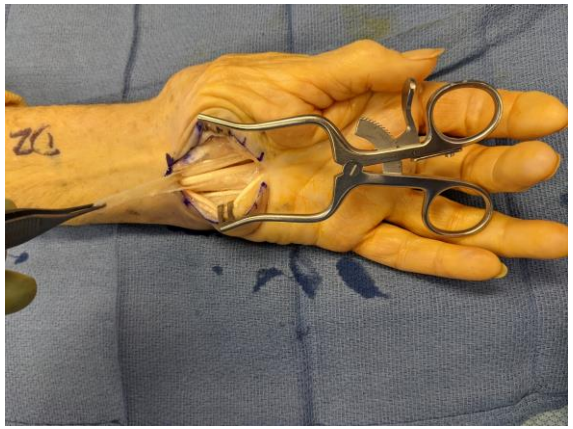
Musculoskeletal Symptoms and Manifestations of ATTR (1/3)

Carpal tunnel syndrome (CTS)

- CTS is frequently bilateral in patients with ATTR and results from amyloid deposits in the flexor tenosynovium and transverse carpal ligament of the hands[1,2]
- Symptoms include: numbness and tingling in thumb, index finger, and middle fingers; discomfort in wrist and palm of hand[2]
  - CTS also occurred prior to development of peripheral neuropathy symptoms in some patients with hATTR[3]

Patient case 1

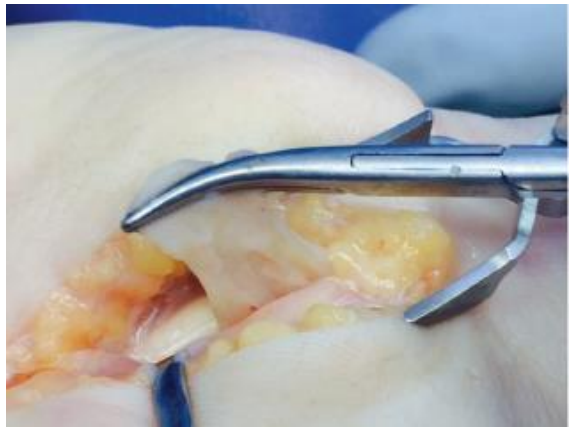


71-year-old male presented with right hand radial 3-digit paresthesias. Patient also had previous back surgery for spinal stenosis and incidence of spontaneous biceps tendon rupture.[4]

Patient case 2

90-year-old male presented with left hand radial 3-digit paresthesias and static numbness. Patient has family history of ATTR amyloidosis and recurrent CTS following previous release surgery.[4]

Patient case 3



67-year-old male presented with symptoms of bilateral CTS and had previous CTS release. Echocardiogram revealed increased septal wall thickness and Tc-PYP revealed grade 3 diffuse myocardial uptake.[1]

ATTR, transthyretin amyloidosis; CTS, carpal tunnel syndrome; hATTR, hereditary ATTR; Tc-PYP, technetium pyrophosphate; TTR, transthyretin.

1. Sperry et al. *J Am Coll Cardiol.* 2018;72:2040–50; 2. Mayo Clinic. Carpal tunnel syndrome. Available from: https://www.mayoclinic.org/diseases-conditions/carpal-tunnel-syndrome/symptoms-causes/syc-20355603 (accessed January 24, 2020); 3. Karam et al. *Neurol Clin Pract.* 2019;9:309–13; 4. Zhang et al. American Society of Surgery of the Hand Annual Meeting. September 30, 2022; Boston MA.

Musculoskeletal Symptoms and Manifestations of ATTR (2/3)

Lumbar spinal stenosis

- TTR amyloid deposits in the ligamentum flavum may be related to the pathogenesis of lumbar spinal canal stenosis in elderly patients[1]
- In one retrospective study, a combination of CTS and spinal stenosis was present in 13% and 2% of patients with wtATTR and hATTR, respectively[2]

Biceps tendon rupture[3]

- Spontaneous rupture of the distal biceps tendon and bunching of the biceps with flexion due to amyloid deposits
- In one cross-sectional study, this was reported in 33% of patients with wtATTR and symptoms of HF
  - Occurred a median of 5 years prior to HF diagnosis

Osteoarthritis

- Approx. 25% of patients with ATTR have a diagnosis of severe osteoarthritis or history of prior joint replacement[4]
- Total knee and hip arthroplasty is 3 to 5 times more common among patients with ATTR than age- and sex-matched controls[5]
  - In a retrospective study of patients with ATTR-CM, 23% (40/172) of patients underwent lower extremity arthroplasty[6]

ATTR, transthyretin amyloidosis; hATTR, hereditary ATTR; wtATTR, wild-type ATTR; CTS, carpal tunnel syndrome; HF, heart failure; TTR, transthyretin.

1. Yanagisawa et al. *Mod Pathol.* 2015;28:201–7; 2. Aus dem Siepen et al. *Clin Res Cardiol.* 2019;108:1324–30; 3. Geller et al. *JAMA.* 2017;318:962–3. 4. Mitter et al. *ISA Congress* 2020. Poster PT135; 5. Ruberg et al. *J Am Coll Cardiol.* 2019;73:2872–92; 6. Rubin et al. *Amyloid.* 2017;24:226–30.

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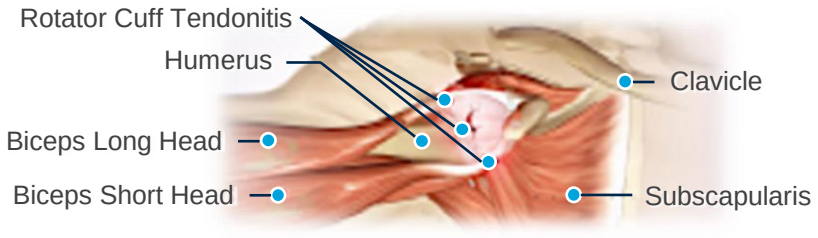
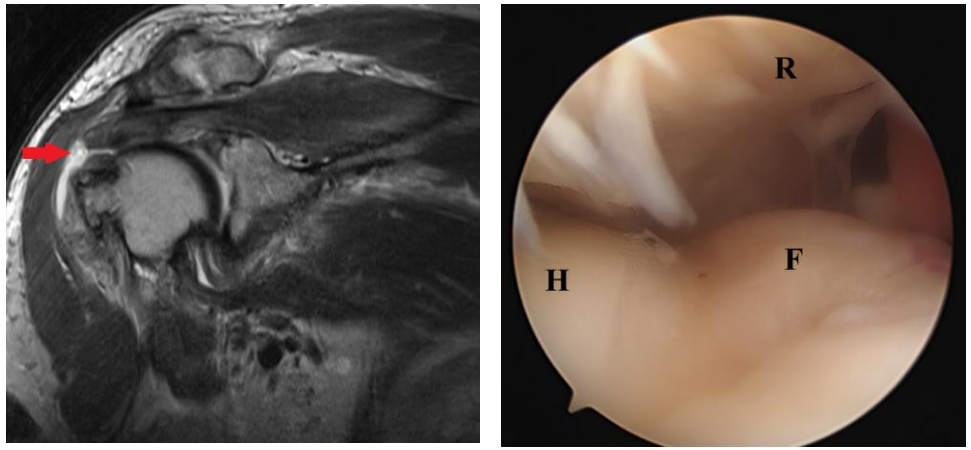
Musculoskeletal Symptoms and Manifestations of ATTR (3/3)

Rotator cuff tear/tendinopathy

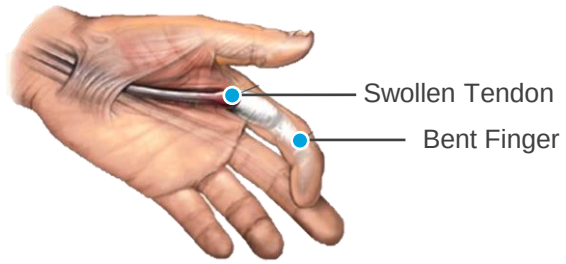
- Among patients undergoing surgery for rotator cuff repair, 38% of tissue samples removed had wtTTR deposits[1,2]
- On average, surgery to repair rotator cuff injury occurs 7.4 to 10.3 years before ATTR diagnosis[3]



Patient case



67-year-old male with wtATTR presenting with a rotator cuff tear as visualized by MRI (left) and arthroscope (right). Patient experienced acute right shoulder pain and had a history of CTS and lumbar spinal stenosis.[4]



Trigger finger/finger tenosynovitis

- Approximately 65% of patients undergoing surgery for finger tenosynovitis show amyloid deposition, with 69% of these cases exhibiting staining for TTR amyloid[5]
- Trigger finger has been reported both in patients with hATTR[6] and wtATTR[7]

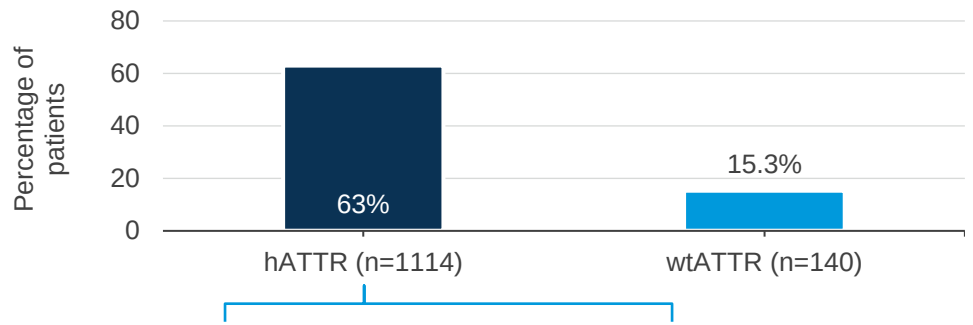
ATTR, transthyretin amyloidosis; hATTR, hereditary ATTR; wtATTR, wild-type ATTR; CTS, carpal tunnel syndrome; MRI, magnetic resonance imaging; TTR, transthyretin.

1. Ruberg et al. *J Am Coll Cardiol.* 2019;73:2872–92; 2. Sueyoshi et al. *Hum Pathol.* 2011;42:1259–64; 3. Campbell et al. *ISA Congress* 2020. Poster PT1194 4. Zhang et al. American Society of Surgery of the Hand Annual Meeting. September 30, 2022; Boston MA; 5. Hara et al. *J Hand Surg Asian Pac. Vol* 2020;25:340–4; 6. Uotani et al. *Intern Med.* 2007;46:501–4; 7. Triguero et al. *Eur J Orthop Surg Traumatol.* 2022;32:575-81

GI Manifestations of ATTR

- hATTR comprises 16% of reported cases of GI involvement in amyloidosis[1]
  - GI involvement is primarily associated with AL amyloidosis
- 59% of all patients with ATTR in the THAOS registry reported at least one GI symptom; symptoms commonly manifest early after disease onset[2]
  - 70.3% of patients with early disease onset (<50 years) reported GI symptoms compared to 49.6% of patients with late disease onset ($P < 0.001$)
- GI manifestations in patients with ATTR include[3]:
  - Upper gastrointestinal symptoms: early satiety, nausea, vomiting
  - Lower gastrointestinal symptoms: constipation, diarrhea, alternating diarrhea and constipation, fecal incontinence
  - Unintentional weight loss
  - Malabsorption and malnutrition

Minimum one GI symptom at THAOS registry enrollment[2]



TTR variant[2]	Patients showing GI symptoms
V30M	69.3%
V122I	27.1%
S50R	65.5%
E89Q	68.4%
T60A	40.0%
F64L	50.0%
S77Y	70.6%
I68L	13.3%
I107V	58.3%
G47A	18.2%
L111M	10.0%

AL, primary/light chain; ATTR, transthyretin amyloidosis; hATTR, hereditary ATTR; wtATTR, wild-type ATTR; GI, gastrointestinal; THAOS, Transthyretin Amyloidosis Outcome Survey.

1. Fritz et al. *Am J Med.* 2022;135:S20–3; 2. Wixner et al. *Orphanet J Rare Dis.* 2014;9:61; 3. Nakov et al. *Eur J Gastroenterol Hepatol.* 2021;33(5):613–22.

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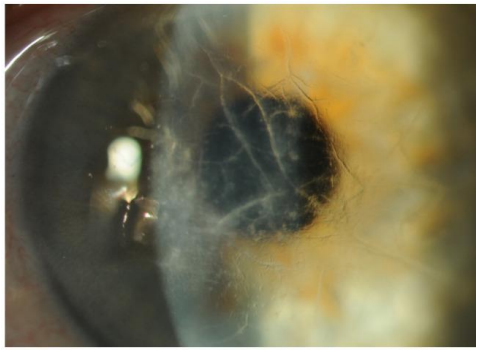
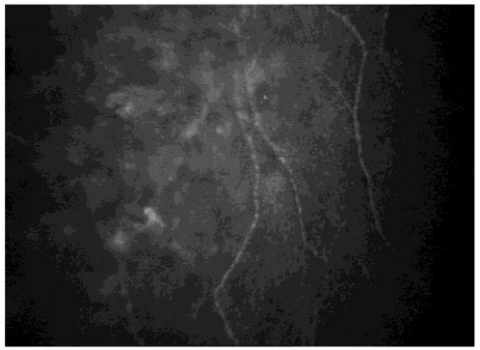
Ocular Manifestations of hATTR

- Common signs and symptoms of ocular involvement in hATTR include[1]:
  - Vitreous opacities/amyloid deposits
  - Pupillary abnormalities
  - Reduced corneal nervous plexa
  - Keratoconjunctivitis sicca
  - Abnormal conjunctival vessels
  - Lens anterior capsule opacities
  - Glaucoma
- Prevalence of ocular manifestations increases with disease duration in hATTR[2]

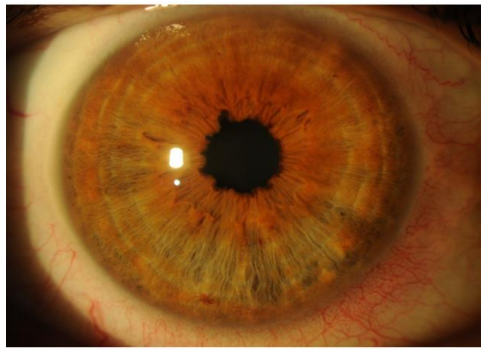
Vitreous opacities/deposits



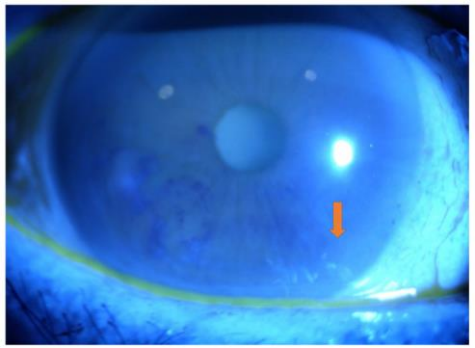
Reduced corneal nervous plexa



Pupillary abnormalities



Keratoconjunctivitis sicca (dry eye)



Images taken from Minnella et al. 2021[1]

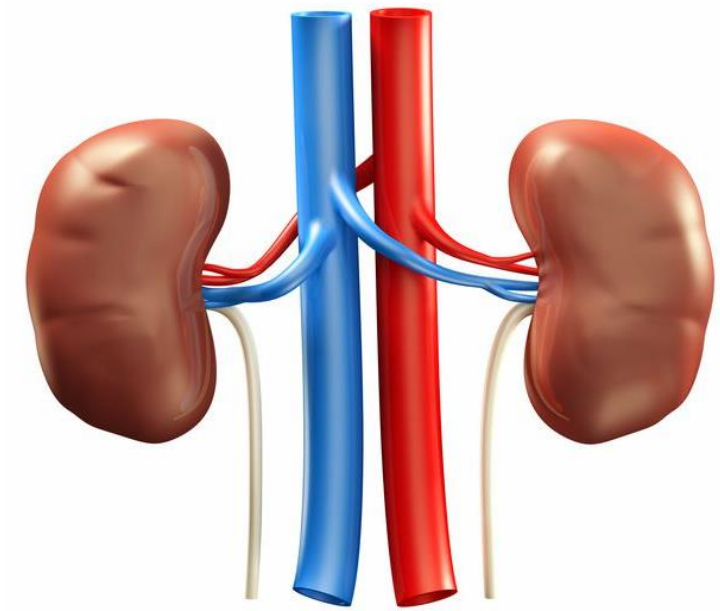
hATTR, hereditary ATTR.

1. Minnella et al. *Genes. (Basel)* 2021;12(7):955; 2. Beirao et al. *Amyloid.* 2015;22:117–22.

Renal Manifestations of ATTR

- Renal involvement is less significant in ATTR-CM compared to AL amyloidosis with cardiomyopathy[1]
  - Cases of chronic kidney disease in both wtATTR and hATTR patients are often a consequence of heart failure[1]
  - The US THAOS registry reported renal impairment in 15% and 20% of wtATTR and V122I hATTR amyloidosis abnormalities may serve as a “red-flag” symptom for hATTR, specifically with polyneuropathy[3,4]
  - While prevalence of renal impairment has been characterized in only a small number of studies, it has been observed in up to 50% of patients with hATTR and across a range of TTR mutations[2,5,6]

Nephropathy signs and symptoms in hATTR[4]



Proteinuria

↓GFR

Renal failure/ insufficiency

AL, primary/light chain; ATTR, transthyretin amyloidosis; hATTR, hereditary ATTR; wtATTR, wild-type ATTR; GFR, glomerular filtration rate; THAOS, transthyretin amyloidosis outcome survey; TTR, transthyretin.

1. Fine et al. *Cad J Cardiol.* 2020; 36:322-34; 2. Maurer et al. *J Am Coll Cardio.* 2016; 68(2):161–72; 3. Conceição et al. *J Peripher Nerv Syst.* 2016;21:5–9; 4. Vaxman and Gertz. *Acta Haematol.* 2020;143(4):304–11; 5. Lobato & Rocha. *Clin J Am Soc Nephrol.* 2012;7:1337–46; 6. Steen et al. *Acta Med Scand.* 1982;212;233–6.

Summary and Next Steps

- ATTR is a multisystemic, rapidly progressive, debilitating, and fatal disease caused by misfolded TTR accumulating as amyloid deposits in multiple organs and tissues including nerves, heart, and GI tract [1-4]
  - Patients diagnosed with hATTR and wtATTR have a median survival of 4.7[5] and 2.5-5.5 years,[6-8] respectively
- ATTR remains underdiagnosed or misdiagnosed[4,9,10]
- Patients with ATTR experience substantial burden, including reduced QoL[11-14] and functional impairment[6,15]

There remains a need for health care professionals to:

1	2	3	4
Recognize the constellation of red-flag symptoms of ATTR[16,17]	**Collaborate with a multidisciplinary team for a potential amyloidosis diagnosis[16,17]**	**Employ the diagnostic algorithm and confirmatory diagnostic tools to verify diagnosis[17-19]**	**Assess progression of disease following treatment and provide patient with holistic care (mental, physical, and social support)[20,21]**

ATTR, transthyretin amyloidosis; hATTR, hereditary ATTR; wtATTR, wild-type ATTR; GI, gastrointestinal; QoL, quality of life; TTR, transthyretin.

1. Hanna. *Curr Heart Fail Rep.* 2014;11:50–7; 2. Mohty et al. *Arch Cardiovasc Dis.* 2013;106:528–40; 3. Adams et al. *Neurology.* 2015;85:675–82; 4. Maurer et al. *Circ Heart Fail.* 2019;12:e006075; 5. Swiecicki et al. *Amyloid.* 2015;22:123–31; 6. Lane et al. *Circulation.* 2019;140:16–26; 7. Aus dem Siepen et al. *Clin Res Cardiol.* 2018;107(2):158–69; 8. Givens et al. *Aging health.* 2013;9(2):229–35; 9. Hawkins et al. *Ann Med.* 2015;47:625–38; 10. Castano et al. *Heart Fail Rev.* 2015;20:163–78; 11. Coehlo et al. *Muscle Nerve.* 2017;55:323–32; 12. Vinik et al. *J Peripher Nerv Syst.* 2014;19:104–14; 13. Ines et al. *ISPOR Congress* 2015. Poster N21; 14. Obici et al. *Amyloid.* 2020;27:153–62; 15. Bolte et al. *Orphanet J Rare Dis* 2020;15:287; 16. Nativi-Nicolau et al. *Heart Fail Rev*. 2022;27(3):785–93; 17. Kittleson et al. *JACC.* 2023; 81(11):1076–176; 18. Namiranian and Geisler. *Am J Med.* 2022;135 Suppl 1:S13–19; 19. Ando et al. *Orphanet J Rare Dis.* 2013;8:31; 20. Adams et al. *Orphanet J Rare Dis.* 2021;16:411; 21. Obici et al. *BMJ Open.* 2023;13:e073130.

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