Musculoskeletal Manifestations Associated with ATTR Amyloidosis

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- This resource provides information about musculoskeletal manifestations associated with ATTR amyloidosis.
- 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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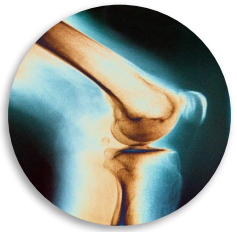
A Range of Systemic Amyloidoses Exist

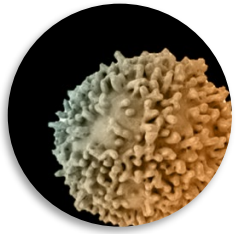
- Amyloidoses are a heterogeneous group of disorders characterized by the deposition of insoluble protein aggregates[a] (amyloid deposits) in tissues[1,2]
  - Amyloidosis can be acquired or inherited, and systemic or localized[3]

The most common types of systemic amyloidosis are categorized by pathogenic proteins[4,5]

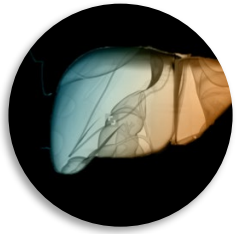
AL type, immunoglobulin light chain



$A\beta_2$-M type, β_2-microglobulin (wild-type and variant)



AA type, (apo) serum amyloid A



ATTR type, transthyretin (TTR) (wild-type and hereditary)

[a]Amyloid deposits consist of misassembled, insoluble protein fibrils that can disrupt normal tissue structure and function

AA, amyloid A; $A\beta_2$-M, β_2 microglobulin; AL, immunoglobulin light chain; apo, apolipoprotein; ATTR, transthyretin-mediated; TTR, transthyretin

1. Shin & Robinson-Papp. *Mt Sinai J Med* 2012;79:733–48; 2. Sipe et al. *J Protein Fold Disord* 2016;23:209–13; 3. Rowczenio et al. *Hum Mutat* 2014;35:E2403–12; 4. Hazenberg. *Rheum Dis Clin North Am* 2013;39:323–45; 5. Damy et al. *Amyloid* 2016;23:194–202

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Clinical Manifestations of ATTR and Other Systemic Amyloidoses[1–3]

Site of Involvement	AL Amyloidosis	AA Amyloidosis	$A\beta_2$-M Amyloidosis	ATTR Amyloidosis[a]
Kidney	+++	+++	–	+
Heart	+++	+	(+)	+++
Peripheral nervous system	++	–	–	+++
Autonomic nervous system	++	(+)	–	+++
Liver	++	++	(+)	–
Spleen	+	++	(+)	–
Musculoskeletal system	++	–	+++	++/+++
Eyes	–	–	–	++
Tongue	+++	(+)	–	–

[a]ATTRwt or ATTRv amyloidosis. Kidney, peripheral and autonomic nervous system, and eye involvement are more common in hATTR amyloidosis than in wtATTR amyloidosis.
+++ = very common; ++ = common; + = rare; (+) = very rare; – = absent
AA, amyloid A; $A\beta_2$-M, β_2 microglobulin; AL, immunoglobulin light chain; ATTR, transthyretin-mediated; ATTRv, hereditary transthyretin (v for variant); ATTRwt, wild-type transthyretin

1. Perfetto et al. *Nat Rev Rheumatol* 2010;6:417–29; 2. Gonzalez-Duarte. *Clin Auton Res* 2019;29:245–51; 3. Wininger et al. *BMC Musculoskelet Disord* 2021;22:51

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Variant/Hereditary and ATTRwt Amyloidosis

hATTR amyloidosis[1,2] (ATTRv amyloidosis)

Amyloid deposits

- Variant TTR
- wt TTR

Multisystem disease

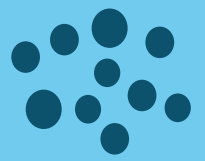
Sensory and motor, autonomic, cardiac, and musculoskeletal symptoms

>120 TTR variants have been reported[5]

Median survival after diagnosis 4.7 years[6] (3.4 years with cardiomyopathy)[6–8]

wtATTR amyloidosis[1,3,4] (ATTRwt amyloidosis/senile systemic amyloidosis)

Amyloid deposits



- wt TTR

Predominantly cardiac symptoms

Other systems can be involved with other manifestations e.g., musculoskeletal symptoms

Median survival after diagnosis 2.5–5.5 years[9–14]

ATTRv, hereditary transthyretin-mediated (v for variant); ATTRwt, wild-type transthyretin; hATTR, hereditary transthyretin-mediated; TTR, transthyretin; wt, wild-type; wtATTR, wild-type transthyretin-mediated

1. Hawkins et al. *Ann Med* 2015;47:625–38; 2. Campbell et al. ISA Congress 2020. Poster PT119; 3. Nakagawa et al. *Amyloid* 2016;23:58–63; 4. Sueyoshi et al. *Hum Pathol* 2011;42:1259–64;
5. Rowcenzio et al. *Hum Mutat* 2014;35:E2403–12; 6. Swiecicki et al. *Amyloid* 2015;22:123–31; 7. Sattianayagam et al. *Eur Heart J* 2012;33:1120–7; 8. Gertz et al. *Mayo Clin Proc* 1992;67:428–40;
9. Lane et al. *Circulation* 2019;140:16–26; 10. Ruberg et al. *Am Heart J* 2012;64:222–8; 11. Connors et al. *Circulation* 2016;133:282–90; 12. Grogan et al. *J Am Coll Cardiol* 2016;68:1014–20;
13. Pinney et al. *J Am Heart Assoc* 2013;2:e000098; 14. Givens et al. *Aging Health* 2013;9:229–35

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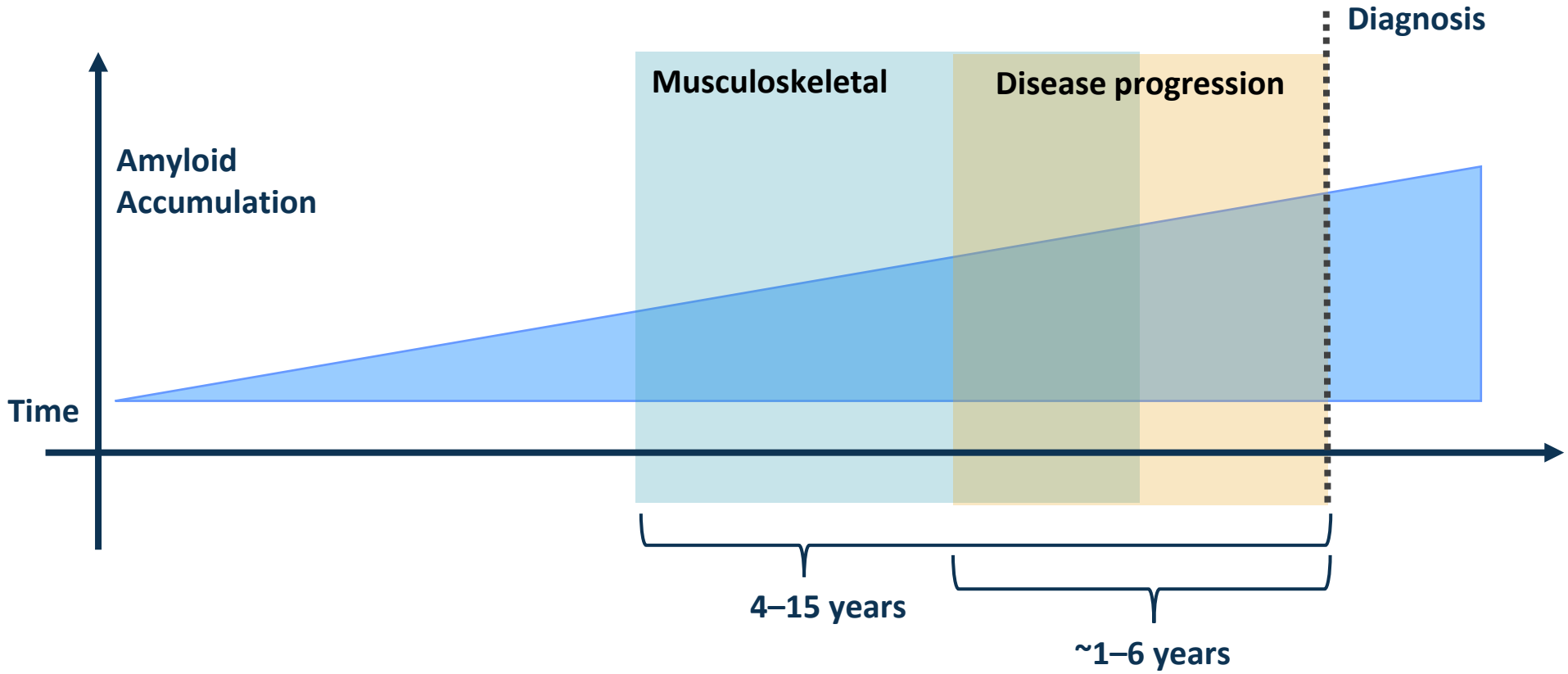
Musculoskeletal Manifestations Can Precede the Presentation of Other Symptoms of ATTR Amyloidosis and Final Diagnosis by Years[1–4]



Understanding the prevalence and characteristics of orthopedic manifestations in ATTR amyloidosis may raise suspicion of the disease, and lead to earlier diagnosis

ATTR, transthyretin-mediated

1. Campbell et al. *ISA Congress* 2020. Poster PT119; 2. Adams et al. *Curr Neurol NeuroSci Rep* 2014;14:435; 3. Swiecicki et al. *Amyloid* 2015;22:123–31; 4. Rozenbaum et al. *Cardiol Ther* 2021;10:141–59

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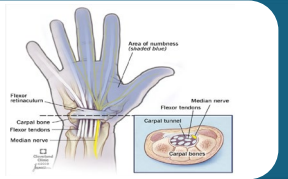
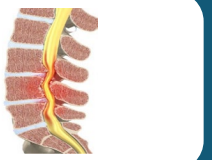
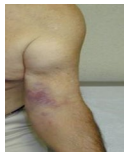
Musculoskeletal Manifestations Identified in Patients with ATTR Amyloidosis[a,1–5]



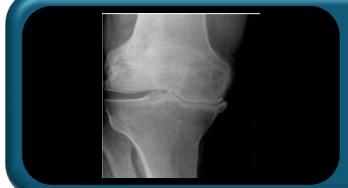
Carpal tunnel syndrome



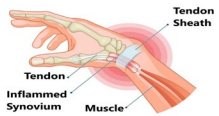
Lumbar spinal stenosis



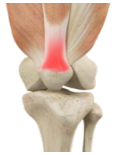
Biceps tendon rupture



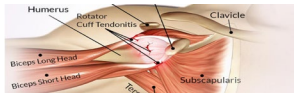
Osteoarthritis



Tenosynovitis



Quadriceps tendinopathy



Rotator cuff tendinopathy

[a]Manifestations also reported in individual case studies
ATTR, transthyretin-mediated

1. Ruberg et al. *J Am Coll Cardiol* 2019;73:2872–92; 2. M'bappe et al. *Best Pract Res Clin Rheumatol* 2012;26:459–75; 3. Hara et al. *J Hand Surg Asian Pac Vol* 2020;25:340–4; 4. Niggemeyer et al. *Arch Orthop Trauma Surg* 2011;131:637–43; 5. Mitter et al. *ISA Congress* 2020. Poster PT135

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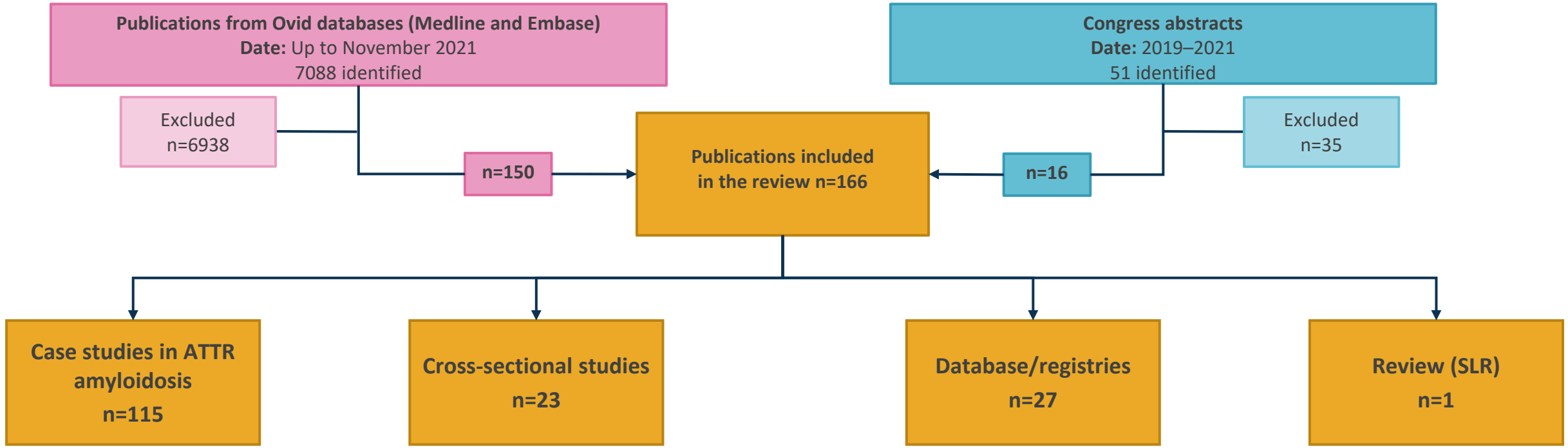
Literature on Musculoskeletal Manifestations of ATTR Amyloidosis is Significant

Search terms
Topic: Musculoskeletal manifestations associated with ATTR amyloidosis; epidemiology, pathophysiology, temporal association, burden, and current clinical practice
Study types: Epidemiologic, cross-sectional, retrospective cohort, prospective cohort, case control, reviews with and without meta-analysis, and RCTs



The literature highlighted a strong association between ATTR amyloidosis and musculoskeletal manifestations, particularly CTS

An SLR was conducted using Medline and Embase. Relevant conference proceedings were also searched. Publications were screened for inclusion using pre-specified PICOTS criteria
ATTR, transthyretin-mediated; CTS, carpal tunnel syndrome; PICOTS, patient, intervention, comparator, outcome, time, study; RCT, randomized controlled trial; SLR, systematic literature review

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Prevalence at Diagnosis or History of Musculoskeletal Manifestations in Patients with ATTR Amyloidosis

Manifestation or Surgery	ATTRwt Amyloidosis	ATTRv Amyloidosis
CTS	25–65%[1–6]	29–56%[4,6–12]
Lumbar spinal stenosis	14–24%[2,6,7]	5–26%[6,7]
Osteoarthritis or hip/knee surgeries with TTR amyloid	25%[7]	26%[7]
Biceps tendon rupture	33%[13]	—

CTS is the most frequently reported orthopedic manifestation identified in ATTR amyloidosis

ATTR, transthyretin-mediated; ATTRv, hereditary transthyretin (v for variant); ATTRwt, wild-type transthyretin; CTS, carpal tunnel syndrone; TTR, transthyretin; wt, wild-type

1. Pinney et al. *J Am Heart Assoc* 2013;2:e000098; 2. Sekijima et al. *Amyloid* 2018;25:8–10; 3. Galat et al. *Eur Heart J* 2016;37:3525–31; 4. Milandri et al. *Eur J Heart Fail* 2020;22:507–15; 5Nakagawa et al. Amyloid 2016;23:58–63; 6. Aus dem Siepen et al. *Clin Res Cardiol* 2019;108:1324–30; 7. Mitter et al. *ISA Congress* 2020. PT135; 8. Gagliardi et al. *Eur J Heart Fail* 2018;20:1417–25; 89. Damy et al. *Eur Heart J* 2016;37:1826–34; 10. Cappellari et al. *J Peripher Nerv Syst* 2011;16:119–29; 11. Lousada et al. *Orphanet J Rare Dis* 2017;12(Suppl. 1):P7;
12. Gospodinova et al. *Orphanet J Rare Dis* 2015;10(Suppl. 1):P59; 13. Geller et al. *JAMA* 2017;318:962–3

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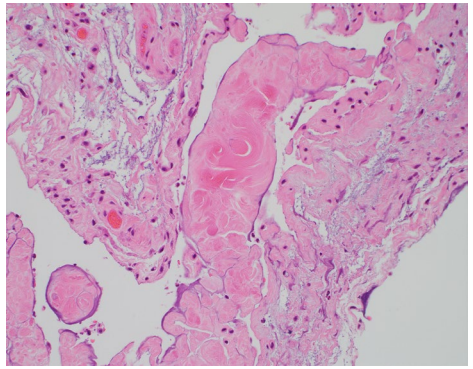
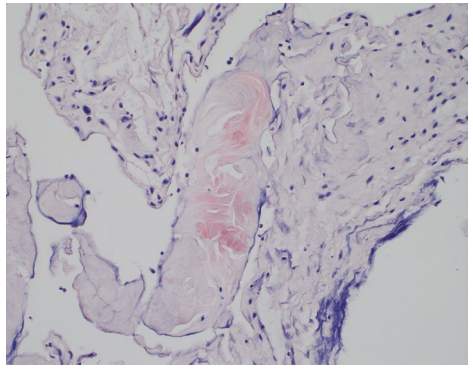
Amyloid Deposits Can Be Detected in Connective Tissue by Congo Red Staining and Confirmed by Mass Spectrometry

Frequency of amyloid deposition in tissues[1,2]

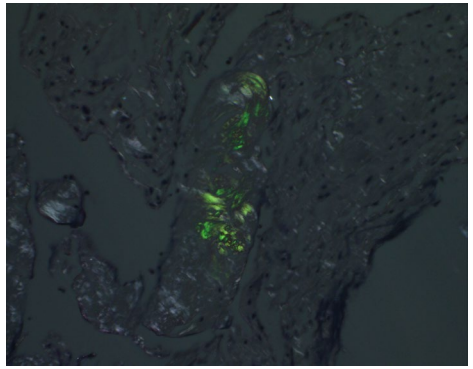
Orthopedic Disorder or Procedure	Total No. of Samples	TTR-Positive Amyloid
CT syndrome (flexor tenosynovium)[1]	54	18 (33%)
CT surgery[2]	727	75 (10%)
CT release surgery[3]	100	13 (13%)
Rotator cuff tears (rotator cuff tendon)[1]	21	5 (24%)
Lumbar spinal stenosis (yellow ligament)[1]	36	16 (44%)
Surgery for lumbar spinal stenosis[4]	250	93 (37%)



Hematoxylin and eosin



Congo red



Polarized light

CT, carpal tunnel; TTR, transthyretin

1. Sueyoshi et al. *Hum Pathol* 2011;42:1259–64; 2. Aus dem Siepen et al. *ISA Congress* 2018. Poster PB048;
3. Bastkjaer et al. *ISA Congress* 2020. Poster PM056; 4. Eldhagen et al. *J Intern Med* 2021;289:895–905

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Proposed Diagnostic Algorithm for Identifying Patients for Further Investigation (Tissue Biopsy and Amyloid Typing[a])

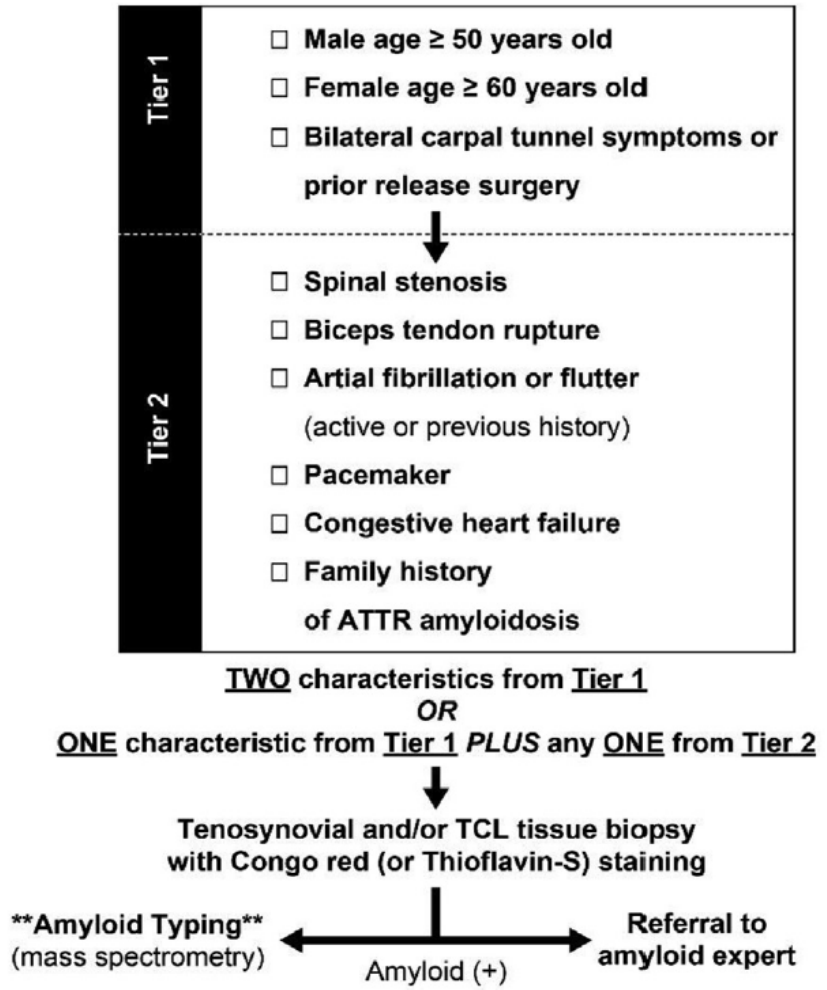
CURRENT CONCEPTS

Carpal Tunnel Syndrome: A Potential Early, Red-Flag Sign of Amyloidosis

Joseph P. Donnelly, MD,* Mazen Hanna, MD,* Brett W. Sperry, MD,*† William H. Seitz, Jr, MD‡

Tier 1 criteria were selected based on a higher prevalence of amyloidosis in older individuals and the observation that CTS is typically bilateral and can recur in patients with amyloidosis, requiring multiple surgical interventions

Tier 2 includes other red-flag symptoms or common characteristics of patients with AL or ATTR



[a]If Congo red or thioflavin staining is positive, then immunohistochemistry or mass spectrometry must be ordered to define the amyloid subtype

AL, amyloid light chain; ATTR, transthyretin-mediated; CTS, carpal tunnel syndrome; TCL, transverse carpal ligament

Donnelly et al. *J Hand Surg Am* 2019;44:868–76. Figure adapted from Sperry et al. *J Am Coll Cardiol* 2018;72:2040–50. Reprinted from J Am Coll Cardiol, 72/17, Sperry BW, et al, Tenosynovial and cardiac amyloidosis in patients undergoing carpal tunnel release, 2040–50, Copyright (2018), with permission from Elsevier

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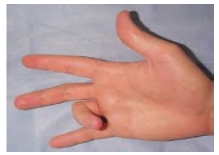
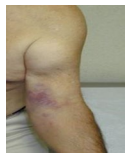
Surgeons Are in a Unique Position for Early Detection of Amyloidosis

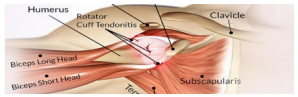
Red-flag manifestations and diagnoses that may prompt the orthopedic surgeon to biopsy or refer for amyloidosis



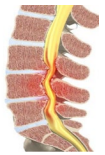
Trigger finger



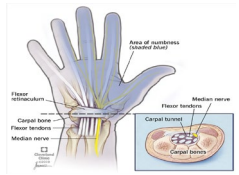
Spontaneous distal biceps rupture



Rotator cuff disease



Lumbar spinal stenosis



Carpal tunnel syndrome

Zhang et al. *J Am Acad Orthop Surg* 2021;29:e488–96

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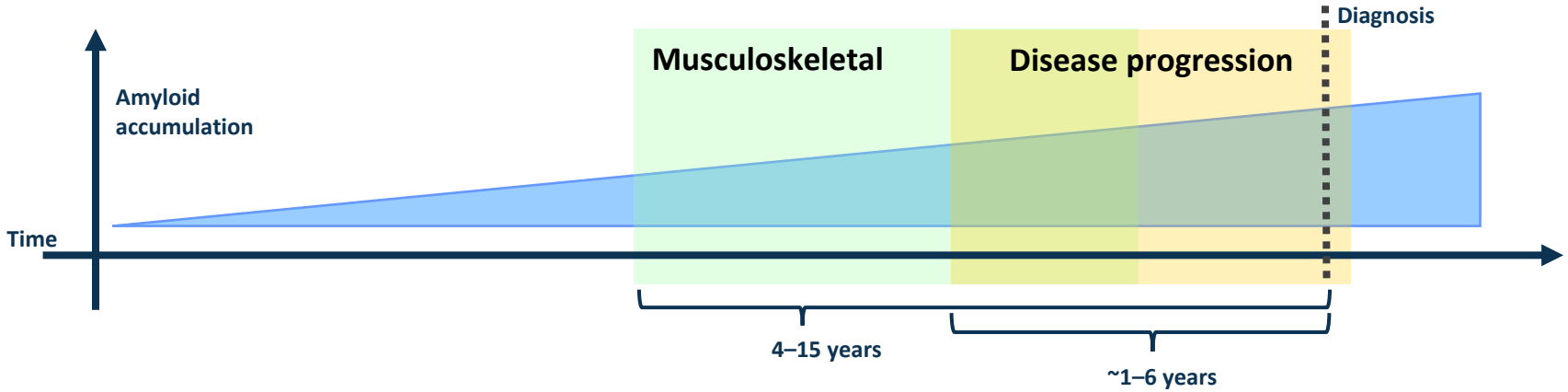
Summary

- ATTR amyloidosis is an underdiagnosed, rapidly progressive, debilitating, and fatal disease caused by misfolded TTR protein that accumulates as amyloid fibrils in multiple tissues (e.g., nerves, GI tract, musculoskeletal)
- Musculoskeletal manifestations and related surgical procedures can precede disease progression and amyloidosis diagnosis by years
- Amyloid deposits can be detected in connective tissue by Congo red staining and confirmed by mass spectrometry
- Surgeons are in a unique position for early detection of amyloidosis



ATTR, transthyretin-mediated; GI, gastrointestinal; TTR, transthyretin

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