

Klinik für Neurologie

Neuromuskuläres Zentrum

Amyloidosis: Neurology

J.A. Petersen



UniversitätsSpital
Zürich

Systemic Amyloidosis: Classification

<i>Primary Amyloidosis (AL)</i>	<i>Primary systemic amyloidosis Multiple-myeloma-associated</i>	<i>Monoclonal light chain, kappa or lambda</i>
<i>Hereditary Amyloidosis</i>	<i>Familial amyloid neuropathy</i>	<i>due to pathologic serum proteins</i>
<i>Secondary Amyloidosis (AA)</i>	<i>due to infection or inflammation</i>	<i>Protein A</i>

Peripheral nervous system involvement is not a significant part of the clinical presentation of AA Amyloidosis

Senile amyloidosis

Dialysis-associated amyloidosis

Primary systemic Amyloidosis: Polyneuropathy

Kidney:	32% (nephrotic)
Median nerve:	24% (carpal tunnel)
Heart:	23% (congestive heart failure, cardiomyopathy)
Peripheral nerves:	17% (peripheral neuropathy)
Autonomic neuropathy:	14% (orthostatic dizziness, fainting, diarrhea, bladder dysfunction, impotence)

(Kyle and Gertz, Crit Rev Oncol Hemato1990)

Primary systemic Amyloidosis: Polyneuropathy

Most patients have major systemic disease and neuropathy is diagnosed as a result of ENMG screening (Matsuda et al Eur J Neurol 2011)

However, peripheral neuropathy is the most common initial neurologic manifestation (Kelly et al 1979; Kyle and Greipp 1983)

43 patients with primary systemic AL amyloidosis (Matsuda et al Eur J Neurol 2011)

Polyneuropathy is symmetrical and sensory-dominant

Motor weakness was rare

Early stage: painful paraesthesia of the distal legs

Late stage: autonomic dysfunction (orthostatic hypotension...) (other studies: early stage)

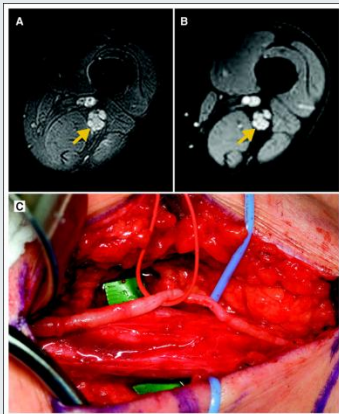
Late age at onset

Primary systemic Amyloidosis: other neuropathies

Upper extremity Neuropathy due to biopsy proven primary amyloidosis with no systemic or autonomic features (Tracy et al. Muscle Nerve 2010)

Rare cases present with focal nerve involvement (Amyloidomas) resulting in compression or light chain deposition in the nerve (sciatic nerve, lumbosacral roots, plexus)

Asymmetric mononeuritis multiplex resembling neuritis (Sadek et al. Journal of clinical oncology 2010)



The mechanism of nerve damage is unknown but possibilities include ischemia and autoantibodies targeted to peripheral nerves

Sciatic nerve demonstrates nodularity with enlargement of individual fascicles

Sadek I et al. JCO 2010;28:e429-e432

©2010 by American Society of Clinical Oncology

Systemic Amyloidosis: other neuropathies

Carpal tunnel syndrome may be the presenting feature. (Kyle and Gertz, Crit Rev Oncol Hemato 1990)

Primary amyloidosis rarely involves cranial nerves (Little et al. South Med J. 1986, Antoine et al. Rev Prat 2008)

In one series, six patients with cranial neuropathies were described, three of them had multiple cranial neuropathies and all of these had length-dependent polyneuropathies (Traynor et al. Ann Neurol. 1991)

In one series, one patient out of 31 had anosmia (Kelly et al, Ann Neurol 1979)

Despite amyloid deposition, palpably enlarged nerves are uncommon (Wang et al, Mayo Clin Proc 2008)

Systemic Amyloidosis: Myopathy

Rarely, generalized amyloidosis can present as myopathy (Friedman et al, Muscle & Nerve 2007)

- 74 year old man with progressive weakness in his back muscles (axial myopathy)
- Serum electrophoresis: monoclonal gammopathy
- amyloid light chain deposition surrounding muscle fibres and vessels in association with vasculitis

Clinical presenting features of patients with muscle weakness and evidence of amyloid deposition within skeletal muscle (Chapin et al. Muscle Nerve 2005; Prayson et al. Hum Pathol 1998)

- proximal muscle weakness is the most common finding (90% of patients)
 - CK levels are mostly normal (2/3 of cases) but may be several-fold greater
 - monoclonal protein found in serum or urine in the majority of patients
-
- an atrophic form also exists (without macroglossia and pseudohypertrophy, “Limb-girdle”-phenotype)
 - a small proportion of patients (10%) presents with distal predominant weakness.
 - Atrophy of the finger flexors might be the presenting symptom (Smestad et al., Muscle Nerve 2004)
 - Cases of amyloid myopathy involving the respiratory muscles and resulting in respiratory failure has been reported (Ashe et al. JNNP 1992)

Hereditary Amyloidosis

3-5% of patients with amyloidosis have the hereditary form

There are many types of hereditary amyloidosis determined by the protein that makes up the amyloid deposit: Transthyretin (TTR), Apolipoprotein AI (Apo AI), Gelsolin, Apolipoprotein AII, Fibrinogen...

TTR, Apo AI and Gelsolin form fibrils that result in familial amyloid neuropathy (FAP).

Autosomal-dominant inheritance, variable age at onset, variable penetrance

Transthyretin-Amyloidosis

FAP: patients in whom peripheral or autonomic neuropathy is the predominant clinical manifestation
- variable age at onset / clinical presentation / penetrance within and between different ethnic groups

FAP Type I: Portugese-Swedish-Japanese type

Mutation Val30Met in the TTR gene: gene frequency is 1:585 in northern portugal (US whites: 1:100.000 to 1:1.000.000)

Early: sensorimotor polyneuropathy of the legs; CTS; autonomic dysfunction (constipation / diarrhea / impotence)

Late: Cardiomyopathy, Vitreous opacities, Nephropathy

FAP Type II: Indiana/Swiss; Maryland/German Type

Variety of TTR mutations (Ile84Ser)

Early: CTS

Late: sensorimotor polyneuropathy, autonomic dysfunction (constipation / diarrhea / impotence), cardiomyopathy, vitreous opacities, nephropathy

TTR leptomeningeal / CNS amyloidosis: leptomeningeal / oculoleptomeningeal with dementia, seizures, stroke-like episodes, ataxia, myelopathy, deafness, radiculopathy, and subarachnoid hemorrhage, Psychosis...

Apo A1- and Gelsolin Amyloidosis

FAP Type III (Iowa type): chronic renal failure ist the most common manifestation

Peripheral neuropathy only with Apo A1 Gly26Arg mutation; autonomic dysfunction

FAP Type IV (Finnish-Danish type): Gelsolin gene point mutation

Gelsolin gene point mutation Asp187Tyr

Main symptoms: cranial neuropathies, corneal lattice dystrophy, cutis laxa, mild peripheral neuropathy, autonomic neuropathy, bulbar weakness, aspiration, Carpal tunnel syndrome, brain / spinal cord involvement

Systemic Amyloidosis: Polyneuropathy

In patients with predominant neuropathy, delay to diagnosis of amyloid is much greater (Kelly et al. 1979, Kelly 2006).

Median age at diagnosis 64 years; median duration of symptoms 29 months (Rajkumar et al. Am J Med 1998)

- Constitutional symptoms or systemic illness
 - Generalized weakness
 - Fatigue
 - Weight loss
- Other organ system involvement
 - Congestive heart failure
 - Nephrotic syndrome
 - Renal failure
 - Hepatomegaly
 - Macroglossia
- Prominent small fiber or autonomic neuropathy
- Family history of neuropathy
- Living in or having ancestors from an endemic area

(Simmons et al. J Clin Neuromuscular disord 2007)

- Family history may be negative in patients with hereditary amyloidosis
 - Variable age of onset
 - Incomplete penetrance
- A monoclonal protein may be absent in patients with primary systemic (AL) amyloidosis
- A distal nerve biopsy (most commonly sural nerve) may not demonstrate staining for amyloid
 - Biopsy of other involved tissue may be needed
 - Proximal nerve biopsy may be needed
- Staining for amyloid does not differentiate primary from hereditary amyloidosis
 - Immunohistochemical staining of the biopsy is needed
 - Molecular genetic testing of blood is confirmatory

- Serum and urine immunofixation or immunoelectrophoresis
- Radiologic bone survey
- Evaluation for renal and cardiac involvement
 - Creatinine
 - Urinalysis
 - Echocardiogram
 - Electrocardiogram
- Electrodiagnostic studies
 - If normal, consider tests for small fiber or autonomic neuropathy
- Biopsy
 - Distal nerve
 - Other involved tissue
 - Proximal nerve
 - Immunohistochemical staining
- Blood for mutation analysis in cases of familial amyloidosis

Neuromuskuläres Zentrum Zürich

