Neurological Manifestations of Amyloidosis

Dr Roshanak Tirdad, MD
Neurologist
INTRODUCTION

- Amyloidosis is the general term used to refer to the extracellular tissue deposition of fibrils composed of low molecular weight subunits of a variety of proteins, many of which circulate as constituents of plasma. These deposits may result in a wide range of clinical manifestations depending upon their type, location, and the amount of deposition.
Subtypes of amyloidosis include:

- **AL amyloidosis**: The most common type of amyloidosis in developed countries, Nervous system involvement
- **AA amyloidosis**: secondary amyloidosis
- **Hereditary amyloidosis (familial amyloidosis)**: This inherited disorder often affects the nerves
- **Wild-type amyloidosis**: senile systemic amyloidosis, It can also cause carpal tunnel syndrome.
- **Localized amyloidosis**: better prognosis
Localized Type

• In localized forms, amyloid can be deposited in the brain (hereditary cerebral hemorrhage with amyloidosis of the Icelandic and the Dutch type, and Alzheimer disease), or in the endocrine system (medullary carcinoma of the thyroid).
• A review of literature little mention involvement of nervous system in secondary Amyloidosis.
• In review articles, neurologic deficit was 13.6%.
• This paper indicated that approximately 15% had complaints referable to nervous system.
Pathologic Features in primary systemic type:

• The parenchyma of Brain and spinal cord is uniformly spared of deposition (in single case Report gross and microscopic changes in cerebral cortex)
• The meninge specially Dura matter shows infiltration (change is in vessels)
• Autonomic Ganglia, spinal nerve roots and peripheral nerves consistently show the greatest degree of involvement.
• Although Neurologic signs and symptoms are not uncommon, this disease in sporadic form rarely presents primarily as a Neurologic syndromes
Neurologic Manifestation in AL Type

- Musculoskeletal involvement
- Arthropathy
- Osteopathy
- Nerve involvement
Muscle Involvement in AL type

Visible enlargement (Pseudohypertrophy) in 25%

Macroglossia or lateral scalloping of the tongue is characteristic of AL type and may be the presenting feature (23%)

Myopathy as initial presentation, myalgia 33%, jaw claudication 25%, hoarseness 18%
Amyloid Myopathy as an initial manifestation of Primary AL associated amyloidosis is an uncommon presentation of the disease. A subset of patients may present with proximal muscle weakness with predominant bulbar muscle involvement and may precede the diagnosis of primary systemic amyloidosis by a long time.
• Muscle involvement is associated with widespread or systemic disease and median survival is about 12 month.
• Elevation of cardiac troponin T in the absence of cardiac involvement is a good indicator of muscle involvement in AL type.
Arthropathy due to AL type

- Amyloid deposits can involve the synovium, leading to rheumatic symptoms.
- Low grade, subacute, progressive and symmetric with predilection for the shoulder, knees, wrist and MCP with little morning stiffness with mild or NO tenderness (distinguish AL Type from RA)
- Hand involvement is associated with CTS(13%)
• Soft tissue swelling in 75% specially around glenohumeral joint (shoulder pad)
• When hand is involved, there may be nodularity and thickening of the palmar fascia, 50% of patients developing flexion contracture and weakness.
Osteopathy

- Localized solitary or multiple osteolytic lesions of bone containing Amyloid.
- These lesions may lead to pathologic fractures and bone pain.
AL amyloidosis and peripheral neuropathy

- Amyloid neuropathy can be present in about 17–35% of patients with AL amyloidosis and is the presenting manifestation in 10%.

- It is a progressive, usually painful sensory polyneuropathy, with or without autonomic dysfunction. Neuropathy may be asymmetric, worse distally than proximal, with lower limbs being affected earlier than upper limbs (i.e., length-dependent neuropathy). Pain and temperature sensation are lost before light touch or vibratory sense and motor neuropathy tends to appear after sensory loss.
Patients typically complain of burning, painful electrical sensations as well as symptoms of carpal tunnel syndrome, which may be present in up to 25% of patients and is due to amyloid deposition in the flexor retinaculum.

Electrophysiologic studies show an axonal, sensory greater than motor neuropathy.

Autonomic neuropathy: is frequently present. It may present with symptoms due to orthostatic hypotension, impotence, bladder dysfunction, or gastrointestinal dysfunction. Symptomatic treatment with elastic stockings, fluorinated steroids, or dihydroergotamine may be helpful in patients with orthostatic hypotension.
• Lower Urinary Tract Symptom: generally appear early in the course of amyloid neuropathy and are present in 50 percent of patients within the first 3 years of the disease. Patients most often complain of difficulty in bladder emptying and incontinence, although bladder dysfunction may be asymptomatic.
Transthyretin (TTR) Amyloidosis:
Familial transthyretin related amyloidosis (fATTR)

• Neurological manifestations, particularly polyneuropathy are the most common manifestations of some of the mutations.
Familial amyloid polyneuropathy (FAP)

- If untreated, patients will have progressive neuropathy and disability resulting in death 10–15 years after disease onset.
- Early onset disease (age < 50), which is more common in endemic regions of Japan and Portugal has a high penetrance and presents with a progressive polyneuropathy predominantly involving the small fiber nerves, which is typically manifested by loss of distal pain and temperature sensation, and progressive autonomic dysfunction;
- the latter includes orthostatic hypotension, neurogenic bladder, erectile dysfunction and impaired bowel function (malabsorption, diarrhea and constipation).
• Late onset cases may not have significant clinical dysautonomia, and often present with a progressive distal neuropathy involving large and small fiber modalities, presenting with motor weakness and loss of vibratory and position sense early on, often with significant neuropathic pain.

• Autonomic dysfunction was the initial manifestation of 48% of early onset and 10% of late onset FAP in a previous study. Late onset FAP is often misdiagnosed for more common entities in that age group such as idiopathic neuropathy or chronic inflammatory demyelinating polyneuropathy (CIDP) partly because of lack of positive family history and autonomic symptoms.
Unusual neuropathy phenotypes of FAP include upper extremity onset, ataxic and motor predominant.

One kind of mutation is characterized by a non-length dependent sensory loss and motor deficits, often rapidly progressive disease, and lack of positive sensory symptoms.

As effective treatments are now available for FAP, it is very important to diagnose it in early stages, and before the cardiovascular and neurological disability are not severe.
• Presence of “red-flag” symptomatology have been emphasized to expedite the diagnosis, these include

• positive family history for neuropathy, unexplained heart disease including but not limited to atrial fibrillation, cardiac hypertrophy on echocardiography, carpal tunnel syndrome, gastrointestinal symptoms (anorexia, constipation, diarrhea, nausea, vomiting and unexplained weight loss, alternating constipation and diarrhea), renal involvement (proteinuria and renal failure) and ocular disease. The presence of >1 of the aforementioned features should prompt genetic testing
Familial leptomeningeal and oculomeningeal amyloidosis

• are rare neurological manifestations of fATTR
• Symptoms include stroke, subarachnoid hemorrhage, dementia, hydrocephalus, ataxia, seizures, and sensorineural hearing loss. MRI studies may demonstrate leptomeningeal enhancement and superficial siderosis (sequela of intracranial bleedings) and there may be markedly elevated CSF protein
**Ocular manifestations**
- Vitreous opacification
- Glaucoma
- Abnormal conjunctival vessels
- Papillary abnormalities

**CNS manifestations**
- Progressive dementia
- Headache
- Ataxia
- Seizures
- Spastic paresis
- Stroke-like episodes

**Cardiovascular manifestations**
- Conduction blocks
- Cardiopulmonary
- Arrhythmia
- Mild regurgitation

**GI manifestations**
- Nausea & vomiting
- Early satiety
- Diarrhea
- Severe constipation
- Alternating episodes of diarrhea & constipation
- Unintentional weight loss

**Renopathy**
- Proteinuria
- Renal failure

**Carpal tunnel syndrome**

**Peripheral sensory-motor neuropathy**
Typically axonal, fiber length-dependent, symmetric, and relentlessly progressive in distal to proximal direction

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

• Patisiran and inotersen are approved by the US Food and Drug Administration (FDA) for treatment of polyneuropathy caused by hereditary transthyretin-related amyloidosis (hATTR) in adults, and tafamidis is approved for transthyretin-mediated amyloid cardiomyopathy (ATTR-CM).
Patisiran

• This medication is **used** to treat nerve problems due to a certain inherited condition (transthyretin-mediated amyloidosis). This condition causes a protein that your body normally makes (transthyretin-TTR), to change shape and build up in different parts of your body, which can affect the nerves, heart, and gut.
Onpattro (patisiran) is a double-stranded siRNA that causes degradation of mutant and wild-type TTR mRNA through RNA interference, which results in a reduction of serum TTR protein and TTR protein deposits in tissues.
Current treatment options have limited efficacy and often do not prevent disease progression. Patisiran is a novel RNA interference therapeutic that specifically reduces production of both wild-type and mutant transthyretin protein. In Phase II, III and long-term extension studies in patients with hereditary transthyretin-mediated amyloidosis, patisiran has consistently slowed or improved progression of neuropathy. In addition, the Phase III trial demonstrated significant improvements in quality of life measures and indicators of cardiomyopathy.
Inotersen

• Tegsedi (Inotersen) is a chemically modified antisense oligonucleotide that inhibits the hepatic production of transthyretin (TTR). Several single-point mutations in TTR destabilize its structure, leading to the aggregation and accumulation of amyloid deposits in the nervous system, heart, kidneys and eyes.
• Inotersen, an antisense oligonucleotide inhibitor, was recently approved in the United States and Europe for the treatment of the polyneuropathy
Inotersen is a novel ASO inhibitor that was developed and approved to reduce the production of TTR in patients with ATTRv. Clinical studies showed that weekly SC injections of inotersen provide significant improvements in neuropathy and QoL, which was sustained during long-term follow-up. In addition, inotersen is generally well tolerated with a manageable safety profile, and regular monitoring for thrombocytopenia and glomerulonephritis has been effective based on results from the OLE study.
Tafamidis

- **Tafamidis** is used to treat cardiomyopathy (enlarged and thickened heart muscle) of wild type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce death and hospitalization related to heart problems.
• **Tafamidis** works by slowing the buildup of a certain protein (amyloid fibrils) that causes heart problems. This **medication** is used to treat a certain **type** of heart failure (transthyretin-mediated amyloidosis). It is used to help prevent the heart failure from getting worse and needing treatment in a hospital.
Can they live a normal life with amyloidosis?

- Frequently patients *can* go into remission with drug therapy. In many experiences, the majority of patients surviving the first six months *can* often start recovering thereafter and *can* typically *live normal* or near *normal lives* for years to come.