THAOS®
Transthyretin Amyloidosis Outcomes Survey

PHYSICIAN FACTSHEET

When to suspect TTR amyloidosis

TTR amyloidosis has a variable clinical presentation due to the different types of mutation present, as well as the patient's location (in an endemic or non-endemic region) and age at onset of disease.[1–2]

Difficulty in diagnosing TTR amyloidosis

TTR amyloidosis is commonly misdiagnosed as it is often clinically indistinguishable from other idiopathic polyneuropathies. A crucial step in diagnosing this condition is considering it in the initial differential diagnosis.[3] Physicians should ensure that they question subjects thoroughly to establish the presence of symptoms that may not be volunteered.[1]

Many subjects are often evaluated for years before TTR amyloidosis is recognized as the underlying cause of their symptoms.[1,4] This delay in diagnosis is approximately 4 years[5] and can negatively impact outcomes as the life expectancy of untreated subjects averages only 10 years from symptom onset.[6]

When to consider TTR-FAP

The process of diagnosing TTR-FAP will differ if a subject presents with a family history of disease, compared with if they have no family history.[5]

In subjects with a known family history of the disease, consider TTR-FAP:

- When neurological impairment is apparent in the lower limbs in a subject with a known family history of the disease (e.g. pain and temperature sensation impaired)[3]
- As part of the differential diagnosis in subjects with progressive idiopathic neuropathy[6]
- In subjects with progressive sensory or sensorimotor neuropathy of unknown origin, especially if there is some kind of cardiac involvement (intra-cardiac conduction block), autonomic dysfunction or carpal tunnel syndrome[1]

In subjects without a known family history:

- Four limb involvement and demyelinative features at electromyography (EMG) may indicate TTR-FAP; chronic inflammatory demyelinating polyneuropathy (CIDP) is a common misdiagnosis especially in subjects with little or no autonomic dysfunction[1,6]

The main causes of error associated with a misdiagnosis of CIDP are negative biopsy findings (10% of biopsies are negative); reduced nerve conduction velocity suggesting an axon-demyelinating process; raised cerebrospinal fluid (CSF) protein levels; diffuse areflexia, elevated CSF, and some electromyography findings. Many subjects misdiagnosed with CIDP receive high doses of intravenous (IV) immunoglobulins and corticosteroids. TTR-FAP should be considered if no response is seen with IV immunoglobulins and corticosteroids and neuropathy continues to progress.[5]

Genetic counseling and subsequent testing of subjects displaying progressive, length-dependent axonal neuropathy primarily involving small nerve fibers may help to prevent a misdiagnosis of CIDP.[6] Electron microscopic evaluation, early in the course of disease, may show degeneration of small myelinated fibers and loss of unmyelinated fibers, which is not characteristic of CIDP.[6] In addition, a nerve biopsy may differentiate amyloid from CIDP by revealing deposits that stain with Congo red.[6]

Frequently, a diagnosis of TTR-FAP is not considered in subjects with symptoms of peripheral neuropathy and they are subsequently diagnosed with idiopathic disease. In the absence of a known origin of peripheral neuropathy symptoms, testing for autonomic dysfunction should be considered as this may support identification of the underlying pathogenesis of amyloidosis.[6]

When to consider TTR-CM

Diagnosis of a predominantly cardiac phenotype can be very challenging as subjects present for a wide variety of reasons including symptoms of heart failure, orthostatic hypotension, or abnormalities on electrocardiology in the absence of symptoms – a common misdiagnosis is sarcomeric hypertrophic cardiomyopathy.[1]

Key signs that should raise suspicion of TTR-CM in these subjects are:[1]

- History of carpal tunnel syndrome
- Sensorimotor polyneuropathy
- Unexplained intense myalgia
- Autonomic dysfunction

Assessments

Once suspected, a diagnosis of TTR amyloidosis should be confirmed by genetic testing and biopsy of nerve, subcutaneous fat aspirate, or other affected tissues to confirm the presence of amyloid deposits. A Congo red stain can be used to visualize these as this stain causes amyloid deposits to appear apple green when viewed under polarized light. Protein evaluation of TTR should also be performed.[1]

References

1. Ando Y et al. Guideline of transthyretin-related hereditary amyloidosis from clinicians. *Orphanet Journal of Rare Diseases*. 2013;8:31.
2. Benson MD, Kincaid JC. The molecular biology and clinical features of amyloid neuropathy. *Muscle Nerve* 2007;36:411–423.
3. Planté-Bordeneuve V et al. Diagnostic pitfalls in sporadic transthyretin familial amyloid polyneuropathy. *Neurology* 2007;69:693–698.
4. Zeldenrust SR. In: Gertz MA, Rajkumar SV, eds. Amyloidosis: diagnosis and treatment. Totowa: Humana Press, 2010
5. Adams D et al. FAP neurology and emerging treatments. *Curr Neurol Neurosci* Rep. 2014;14:435–447.
6. Planté-Bordeneuve V, Said G. Familial amyloid polyneuropathy. *Lancet Neurol* 2011;10:1086–1087.