# Transthyretin Familial Amyloid Polyneuropathy Mimicking Chronic Inflammatory Demyelinating Polyneuropathy

*Familial Amyloid Polyneuropathy Case Report*

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## Introduction

Patients with typical Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) experience motor and sensory deficits that progress insidiously over a course of at least eight weeks, with diminished or absent reflexes.[1,2] There have been several revisions to the diagnostic criteria for CIDP over the years to aid clinicians in making this diagnosis, with variable sensitivity and specificity.[3-6] Given this, clinicians need to be aware of red flags that would lead one to consider an alternative diagnosis, such as Transthyretin Familial Amyloid Polyneuropathy (TTR-FAP).[7]

Systemic amyloidosis is caused by pathologic deposition of misfolded proteins, which leads to widespread tissue and organ damage. Amyloidosis can be genetic, acquired by primary hematological disorder, reactive, or related to natural aging.[8] FAP is the most common hereditary form of systemic amyloidosis, which is caused by mutations in TTR, and less commonly apolipoprotein A1, and gelsolin. TTR-FAP is inherited in an autosomal dominant fashion, but has variable penetrance.[9] Yet in late-onset cases, only one-third have a positive family history.[10] Transthyretin is primarily produced in the liver, but a small amount is made in the choroid plexus and retina. It functions to transport thyroxine and retinol binding protein, which incidentally is how the name transthyretin was derived. All known mutations are missense point mutations, that lead to the destabilization of the TTR tetramer and deposition of insoluble TTR oligomeric amyloid protein aggregates. This deposition can cause multiorgan dysfunction, affecting peripheral nerves, heart, liver, eyes, and leptomeninges. Phenotypic variation exists, however TTR-FAP classically presents as a length dependent neuropathy, predominantly small fiber sensory in early-onset cases, in patients prior to age 50. This group also tend to have prominent autonomic and cardiac dysfunction. Late-onset cases are more difficult to identify due to less prominent autonomic symptoms and in twenty percent of cases, a weakness pattern mimicking CIDP.[11]

## Case Report

A 75-year-old right-handed female presented with a 5-year history of progressive extremity numbness and weakness. She first noticed numbness and tingling in her fingers and toes, that progressed to her mid arms and thighs. She also noticed imbalance and difficulty climbing stairs that progressed to weakness in her arms. She also reported unintentional weight loss, orthostasis, and difficulty emptying her bladder. She was previously diagnosed with CIDP, but failed to respond to corticosteroids or IVIG, and was recently placed on azathioprine at an outside clinic. There was no family history of neuropathy. Neurologic exam revealed symmetric moderate proximal and distal extremity weakness, with sparing of cranial and neck musculature. There was atrophy of distal extremities. On sensory examination, pinprick was diminished to elbows and knees, as well as impaired vibratory sense. Romberg was positive. Reflexes were absent to reduced throughout. Gait was wide-based and steppage.

## Electrophysiological Findings

Electrodiagnostic testing showed a moderate mostly symmetric axonal and demyelinating sensorimotor peripheral polyneuropathy (Table 1). We identified > 30% temporal dispersion at left medial nerve (distal and proximal duration 5.4 ms and 7.1 ms, respectively), and increased distal CMAP duration of left ulnar nerve at the wrist (data not shown in the Table) was 7.3 ms. This value was considered prolonged per EFNS/PNS 2010 Criteria since it was ≥ 6.7 ms. In conjunction with the clinical presentation, fulfilled the criteria for definite CIDP based on EFNS 2010 criteria.

## Additional Investigation

Cerebral spinal fluid protein was 73 mg/dL. Given refractoriness to two of the first line therapies for CIDP and due to the presence of mild autonomic symptoms, we evaluated the patient for CIDP mimics and suspected an alternate diagnosis. The patient underwent a sural nerve and vastus lateralis muscle biopsy. The nerve biopsy revealed severe loss of large caliber myelinated never fibers and am-

Table 1: Electrophysiologic Findings. Sensory nerve, motor nerve conduction studies, and need electromyography show asymmetric axonal demyelinating moderate peripheral polyneuropathy. There is left median nerve temporal dispersion along with increased distal CMAP duration of left ulnar nerve that fulfills EFNS 2010 criteria for CIDP. Rec: recruitment, mld: mild, mod: moderate, sev: severe, dec: decreased, ULN: Upper limit of normal, LLN: Lower limit of normal.

| *Sensory nerve conduction* | *Peak Latency [ms] (ULN)* | *Amplitude [μV] (LLN)* | |
|---|---|---|---|
| Median.R to Index | 6.0 (3.7) | 9 (15.0) | |
| Ulnar.R to Digit V | 2.9 (3.1) | 6 (5.0) | |
| Radial.R to Anat Snuff Box | NR (2.8) | NR (10.0) | |
| Sural.R to Ankle | 4.5 (4.5) | 2 (3.0) | |
| Sural.L to Ankle | NR (4.5) | NR (3.0) | |
| *Motor nerve conduction* | *Onset Latency [ms] (ULN)* | *Amplitude [mV] (LLN)* | *Conduction Velocity [m/s] (LLN)* |
| Median.R to APB. Wrist<br>Elbow | 4.9 (4.5)<br>9.9 | 2.8 (4.5)<br>2.7 | 41 (49) |
| Ulnar.R to ADM Wrist<br>B. Elbow<br>A. Elbow | 3.4 (3.6)<br>6.5<br>8.7 | 2.2 (5.0)<br>2.6<br>2.2 | 50 (50)<br>48 |
| Peroneal.R to EDB. Ankle<br>B. Fib Head<br>A. Fib Head | 4.3 (6.6)<br>12.0<br>15.0 | 0.4 (2.0)<br>0.3<br>0.3 | 36 (41)<br>40 |
| Peroneal.R to TA. B. Fib Head<br>A. Fib Head | 3.2 (4.0)<br>6.3 | 1.5 (3.0)<br>1.3 | 37 (40) |
| Tibial.R to AH. Ankle<br>Pop. Fossa | 4.7 (6.0)<br>13.4 | 2.2 (4.0)<br>2.0 | 43 (57) |
| Median.L to APB. Wrist<br>Elbow | 4.4 (4.5)<br>8.6 | 4.8 (4.5)<br>3.4 | 50 (49) |
| Ulnar.L to ADM. Wrist<br>B. Elbow<br>A. Elbow | 3.1 (3.6)<br>6.6<br>8.6 | 4.4 (5.0)<br>4.3<br>3.9 | <br>52 (50)<br>50 |

| *Muscle* | *Act* | *Fibs* | *PSW* | *Fasc* | *Poly* | *Amp* | *Dur* | *Rec* |
|---|---|---|---|---|---|---|---|---|
| Tibialis anterior. R | - | 2+ | 2+ | - | + | + | + | - |
| Gastroc Med H. R | - | 2+ | 2+ | - | + | + | + | mod dec |
| Vastus lateralis. R | - | 1+ | 1+ | - | - | + | + | sev dec |
| Gluteus medius. R | - | 3+ | 3+ | - | + | - | - | mld dec |
| Lumbar paraspinal; low. R | - | 2+ | 2+ | - | | | | |
| 1st dorsal interossei. R | - | 3+ | 3+ | - | + | - | - | mod dec |
| Biceps brachii. R | - | 3+ | 3+ | - | + | - | + | mod dec |
| Deltoid. R | - | 3+ | 3+ | - | + | + | + | mod dec |
| Extensor indicis proprius. R | - | 2+ | 2+ | - | + | + | + | mod dec |
| Triceps brachii. R | - | 1+ | 1+ | Few | + | + | + | mld dec |

yloid deposition within the endoneurium by Thioflavin-S and Congo Red stains (not shown). The muscle biopsy identified clusters of atrophic myofibers. It also revealed amyloid deposition by Thioflavin S and Congo Red stains, and established this as transthyretin via immunohistochemical reaction (Figure 1). Genetic testing for TTR sequence confirmed a point mutation of A to G at position 3861 of allele 1. This mutation led to missense mutation of threonine to alanine at codon position 60, a known pathologic mutation.

To investigate for systemic involvement, an echocardiogram was preformed and demonstrated speckled myocardium, valvular thickening, and moderate concentric left ventricular hypertrophy consistent with amyloid deposition. She was evaluated by our liver transplantation team, but given her widespread disease involvement and age, she was not a candidate for liver transplant. She was started on diflunisal since at the time of her diagnosis, as neither antisense oligonucleotide therapy nor small interfering RNA was available. Genetic counselling was provided and she was lost to follow.

## Discussion

This case highlights the importance of re-evaluation in patients who otherwise fit the diagnostic criteria for CIDP and are either refractory to first line therapies or have unusual manifestations (family history, dysautonomia, etc.). Additionally, this case displays some common clinical features and pitfalls of patients with late-onset TTR-FAP. TTR-FAP is a heterogenous disorder, with wide variation in age of onset, neurologic and systemic manifestations. In late-onset cases, the majority are without a positive family history. Therefore, a clinician needs a high index of suspicion, otherwise there can be significant delay in diagnosis. An accurate and timely diagnosis is particularly important

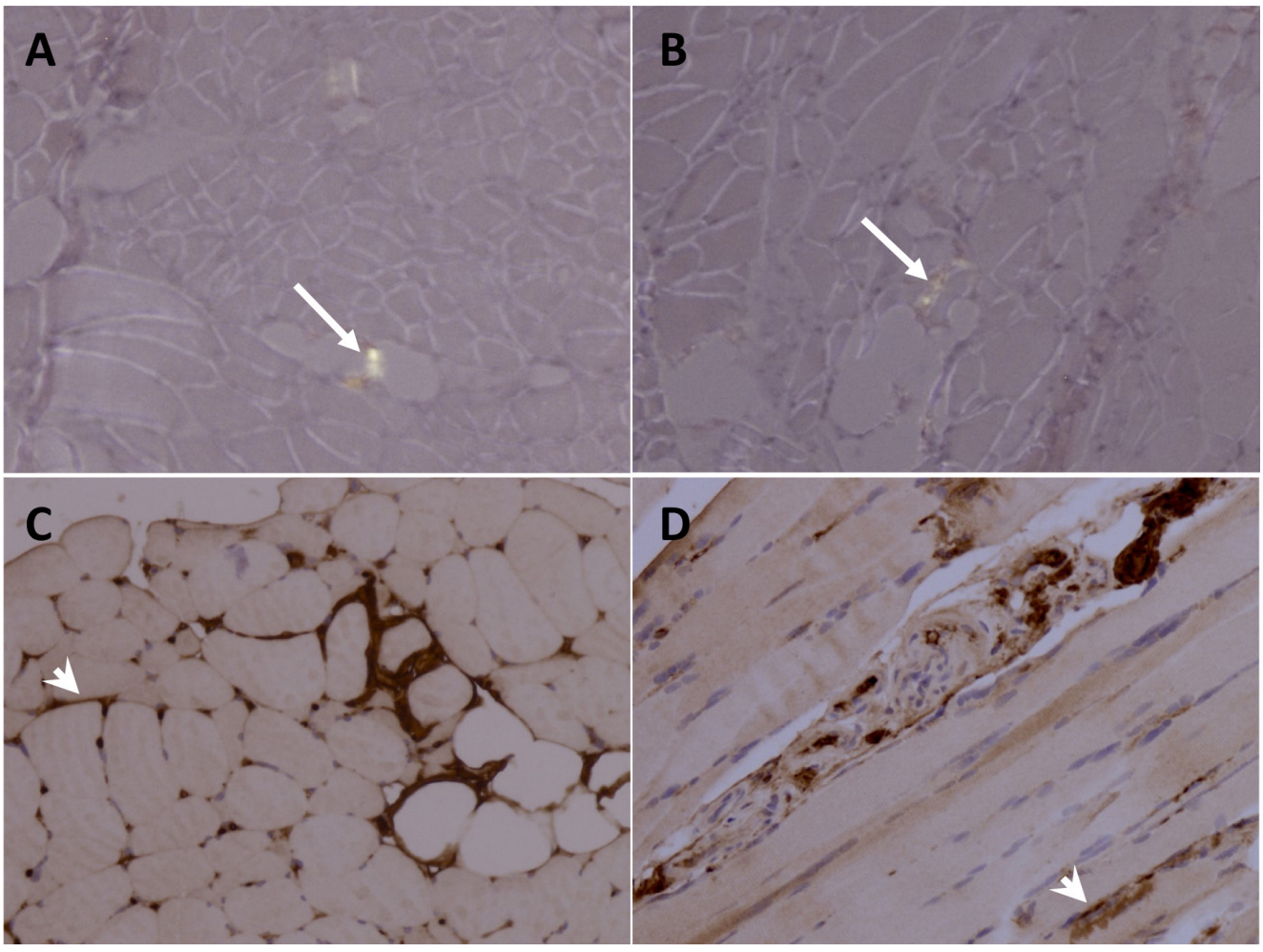


Figure 1. Vastus lateralis muscle biopsy sections. Small amyloid depositions are shown within blood vessel wall (A) and along muscle fiber surface (B) by Congo red stain under polarized light (arrow). Arrowheads in C and D show transthyretin antibody reaction, which identifies amyloid along muscle fiber surface (C) and within muscle cells (D).

since several treatment options are currently available for TTR-FAP.[12-15] In a study of patients presenting with sporadic onset in non-endemic areas, the mean time to diagnosis was four years.[11] In patients with autonomic dysfunction, cardiomyopathy, and lack of response to adequate therapy for CIDP, the diagnosis of TTR-FAP should be considered as to not delay clinical diagnosis, expose patient to unnecessary therapies, nor delay effective novel therapies. Recent expert consensus recommendations to improve diagnosis of TTR amyloidosis with polyneuropathy were published to avoid confusion with CIDP, idiopathic axonal polyneuropathy, lumbar spinal stenosis, and, more rarely, diabetic neuropathy and AL amyloidosis.[16] The challenge in recognition of TTR amyloidosis is more prominent in non-endemic areas, namely outside Portugal, Japan, Sweden, and Brazil. A high index of suspicion is required.

Currently used diagnostic criteria for CIDP are highly sensitive with 80 to 85% specificity. The PREDICT study was a multicenter randomized controlled trial of 6 monthly pulses of dexamethasone versus 8 months of daily prednisolone.[17] In this study, 10/39 (26%) were cured (>5 years off treatment) or in remission according to the CIDP Disease Activity Status scale after 1 or 2 courses of dexamethasone or prednisolone. Despite these CIDP patients being diagnosed by experts and using specified criteria, alternative diagnosis was found 7 out of 12 (58%) cases who did not respond to any therapy included 3 having hereditary neuropathy, 2 malignancy (lymphoma, plasmacytoma),1 TTR-FAP and 1 IgM paraprotein. This suggests a specificity of the ENMC diagnostic criteria for CIDP of 83%.[17,18] In another study, 44% of patients misdiagnosed as CIDP satisfied EFNS/PNS clinical criteria.[19] All of the CIDP misdiagnosis fell in the atypical CIDP group suggesting clinical criteria specificity of 80% (12/59 false positive). In addition, 15% of misdiagnosed patients satisfied EFNS/PNS electrodiagnostic criteria suggesting specificity of the electrodiagnostic criteria to be 93% (4/59 false positive).

While both CIDP and TTR-FAP can have autonomic involvement, these are milder in CIDP. For example, prominent sphincter dysfunction excludes CIDP according to the EFNS/PNS 2010 criteria.[3] In addition, certain features can help differentiate the two clinically. An echocardiogram or cardiac magnetic resonance imaging can be useful to identify evidence of an infiltrative cardiomyopathy, common in TTR-FAP and absent in CIDP. More recently, 99mTechnetium-pyrophosphate imaging (Tc-PYP) is thought to be more sensitive to detect amyloid deposits than other cardiac imaging modalities. In a study of 45 subjects (12 immunoglobulin light-chain amyloidosis [AL], 16 ATTR wild type, and 17 ATTR mutants), Tc-PYP cardiac imaging distinguished AL from ATTR cardiac amyloidosis.[20] Patients can have elevated CSF protein which can be supportive of the diagnosis of CIDP, however TTR-FAP rarely has an elevated CSF protein. In our case, the CSF protein (73) was > 60 mg/dl but many clinicians would consider this level expected for her age of 75. Lastly, 70%-90% of patients with CIDP respond to one or more of the standard therapies, which include corticosteroids, IVIG or plasma exchange.[21] Therefore, lack of treatment response should prompt re-evaluation of the diagnosis.

Recently, Lozeron and colleagues (2018) identified clinical features that could predict demyelinating TTR-FAP.[22] In their cohort, 13 of 84 patients (15%) of French ancestry had late-onset demyelinating TTR-FAP. They identified several suggestive features. Our patient had some of these features including dysautonomia, small fiber sensory loss above the wrists, and upper extremity weakness. Notably, our patient demonstrated sensory ataxia and did not have significant neuropathic pain, which differed from what was found in their demyelinating TTR-FAP cohort.[22]

Our patient was found to have T60A mutation. This mutation is thought to have originated in northwestern Ireland and has now become prevalent in the United States, which it is referred to as Appalachian amyloidosis.[23] It is estimated only 1% of patients worldwide with FAP have this mutation. A prospective study of sixty patients with the T60A mutation showed that a family history of amyloidosis was only present in 37%, median age of symptom onset was 63 years old, and the most common presenting symptom was cardiac.[24] Likewise, cardiomyopathy is nearly twice as common in patients with T60A mutation as compared patients with V30M mutation, the most common mutation worldwide.[23,25] These studies have also demonstrated a link between prevalent cardiac involvement with shorter mean survival. Additionally, non-V30M patients as compared to V30M group have a worse 5-year survival after orthotropic liver transplant. Even after liver transplant, progression of disease has been found to occur, which is thought to be due to wild-type TTR deposition onto existing pathologic amyloid deposits. Thus, the need for alternative therapies exits. Currently there are two TTR stabilizing drugs, tafamidis and diflunisal, and recently approved disease modifying drugs, inotersen and patisiran.[12-15]

## Conclusion

Late-onset proximal and distal weakness, with or without autonomic features, that is refractory to adequate first line therapy for CIDP, despite negative family history should raise clinical suspicion for FAP.

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