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## CLINICAL VIGNETTE

# Gastrointestinal Dysfunction Caused by Familial Amyloid Polyneuropathy

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### Case Report

A 32-year-old female presented for gastroenterology consultation for management of chronic constipation. She had a difficult pregnancy five years prior with nausea, vomiting, and a 20-pound weight loss. After delivery, she felt well for 2 months. However, she developed recurrent nausea and vomiting and difficulty gaining weight. She was evaluated and presumed to have gallbladder disease and underwent cholecystectomy without any improvement. An outside gastroenterologist started amitriptyline 25 mg daily with some improvement in the nausea. However, she had ongoing constipation with infrequent bowel movements and inability to have bowel movements without the use of medication. She was previously treated with polyethylene glycol, lubiprostone, linaclotide, and plecanatide, all of which did not provide relief.

Outside evaluation included gastric emptying study which showed a delay in gastric emptying. Esophagogastroduodenoscopy (EGD) showed esophageal erosions and mild gastritis. Colonoscopy showed internal hemorrhoids but was otherwise normal. CT of the abdomen and pelvis with contrast showed no acute abdominal processes. Anorectal manometry was ordered but not performed due to insurance coverage.

She then developed worsening peripheral neuropathy with gait limitations. She had progressive weakness in bilateral foot dorsiflexion. She was eventually diagnosed with familial amyloid polyneuropathy secondary to V30M amyloid transthyretin (ATTR) based on fat pad biopsies and genetic testing. She then developed exertional shortness of breath, non-cardiac chest pain, and pre-syncope. Baseline ECG showed Mobitz I AV block. Echocardiogram showed no left ventricular hypertrophy or abnormal strain.

The patient was initially started on patisiran and subsequently transitioned to vutrisiran.

### Discussion

Currently there are more than 120 known amyloid transthyretin (ATTR) mutations which include sensory, motor, and autonomic neuropathy.<sup>1</sup> Our patient has the transthyretin amyloidosis, ATTR V30M mutation (also known as Portuguese-type amyloidosis), which is found endemically in the northern parts of Sweden, and in areas of Portugal and Japan.<sup>2</sup> ATTR V30M is the most common form of systemic hereditary amyloidosis with an autosomal dominant inheritance.<sup>3</sup> The disease is also

referred to as familial amyloid polyneuropathy type I (FAP-I) due to a mutation in the transthyretin (TTR) protein from a single amino acid substitution of methionine for valine at position 30 of the TTR molecule (TTR V30M). The disease is characterized by the accumulation of amyloid fibrils in the extracellular milieu of different organs, which include the peripheral nerves, kidney, heart, eye, and gastrointestinal tract.<sup>4</sup>

ATTR is rare with a cumulative estimated number of patients in 2018 of 10,186 (range: 5526-38,468)<sup>5</sup> with a prevalence of 0.052 per 10,000 in Europe.<sup>6</sup> The clinical manifestations generally present in the 3<sup>rd</sup> and 4<sup>th</sup> decades of life. In addition to neurological manifestations, patients may experience cardiomyopathy and nephropathy.

Our patient's gastroparesis and constipation resulted from autonomic neuropathy. The Transthyretin Amyloidosis Outcomes Survey (THAOS), the first global, multicenter, longitudinal, observational survey, reported between 56 and 69% of patients with gastrointestinal (GI) disturbances. Unintentional weight loss (32%) and early satiety (26%) were the most frequently reported symptoms. Patients with early onset disease < 50 years reported gastrointestinal symptoms more frequently than those with late onset, and gastrointestinal manifestations were more common in patients with the V30M mutation compared to those with other mutations. GI disturbances presented before onset of polyneuropathy. GI symptoms included diarrhea and constipation in 24.3% of patients, constipation alone in 20.9% of patients, diarrhea alone in 19.8% of patients, nausea, vomiting, and fecal incontinence.<sup>7</sup> Early satiety, nausea, vomiting, weight loss, and post-prandial fullness are symptoms of gastroparesis which is attributed to autonomic dysfunction.

The treatment of ATTR involves RNA-targeted therapies which interfere with hepatic TTR synthesis reducing the availability of misfolded monomers to aggregate and form amyloid deposits. Patisiran, vutrisiran, inotersen, and eplontersen have been approved by the US Food and Drug Administration (FDA) for treatment of polyneuropathy caused by hereditary ATTR in adults.<sup>8,9</sup> Tafamidis and tafamidis meglumine are approved for transthyretin-mediated amyloid cardiomyopathy. As more than 95% of TTR is produced by the liver, transplantation of the liver is an established treatment. The first liver transplant for this indication was performed in Sweden in 1990.<sup>10</sup>

This case highlights need for increased awareness of ATTR and attention to rare diseases by internists and gastroenterologists in patients presenting with symptoms related to autonomic dysfunction.

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