**CLINICAL VIGNETTE**

# Amyloidosis Presenting as Recurrent Syncope: A Case Report and Discussion

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## *Case Report*

A 53-year-old Iranian American male was in excellent health until 6 months prior to his presentation to UCLA with recurrent syncope. The first episode occurred while he was working in his store when a customer came in requesting assistance. He stood up from a bent over position, ran to the front of the store, and lost consciousness. This was the first of many syncopal episodes. Initially, these occurred roughly weekly, but increased in frequency to two to three times per day. Episodes were generally associated with positional changes from seated or lying to standing. There was no associated palpitations, chest pain, or shortness of breath. There was no clinical history to suggest seizures.

In addition, he developed persistent diarrhea that was refractory to over-the-counter diarrhea therapies. He described it as profuse, watery diarrhea, but without any particular change in odor. He had no associated dietary changes, abdominal pain, fevers, travel history, hematochezia, or melena.

He presented to an outside hospital for evaluation. Work-up included an echocardiogram, carotid Doppler ultrasound, and ECG; all were reported normal. In addition he underwent upper and lower endoscopies, and multiple stool studies that did not reveal a source for the diarrhea.

With no clear explanation he was transferred to UCLA for further work-up and treatment. On presentation, he was a cachectic male who reported 60 lbs of weight loss over the preceding months. He was tachycardic with orthostatic changes in blood pressure, but was otherwise without significant exam findings. Initial routine laboratory testing was also unremarkable. EKG showed a first degree AV-block, but was otherwise normal. Although fluid resuscitation for his diarrheal losses improved his blood pressure and normalized his heart rate, he remained orthostatic. Echocardiogram showed mild concentric LVH, but was otherwise normal without significant valvular or outflow abnormalities. There were no obvious cardiac etiologies. Other studies included normal thyroid and adrenal function, negative ganglionic acetylcholine receptor antibody for autoimmune autonomic ganglionopathy and a PET-CT of the brain negative for Lewy Body dementia.

Urine was remarkable for proteinuria and an SPEP and UPEP revealed a monoclonal protein band. Immunofixation showed monoclonal lambda light chain in the urine. At this point, biopsies from the colonoscopy at the outside hospital were available and documented amyloidosis of the colon.

## *Discussion*

Amyloidosis can be a somewhat confusing disorder, in that it is a collection of different underlying physiologic problems presenting with a shared pathologic finding – amyloid deposition. Further, many of these underlying disorders can present with non-amyloid pathology.

The key property that makes a protein amyloidogenic is the ability to form an abnormal beta-pleated sheet conformation and aggregate into a fibrillary structure that is both insoluble and resistant to proteolysis[1,2]. As the protein deposits in tissues, it is not readily re-absorbed and collects in large quantities. Injury occurs primarily by either impairment of normal diffusion to the affected cells or by physical compression of parenchymal cells[1]. The property to form these deposits is most commonly found in light chains of immunoglobulins[2]. A plasma cell has the potential to produce amyloid deposits if it generates immunoglobulin with light chains. If the plasma cell is part of a persistent monoclonal population (i.e., a plasma cell dyscrasia) it may generate sufficient quantities of this amyloidogenic light chain to lead to deposition and amyloid formation in various tissues—or amyloidosis[1]. Light chain amyloidosis is referred to as AL amyloid.

There are other proteins that may also have amyloidogenic properties – that is the ability to form these particular beta-pleated sheets. Certain variants of the acute phase protein serum amyloid A protein (SAA) have the potential to collect and stack as amyloid deposits. Either a genetic predisposition as is seen in familial Mediterranean fever, or severe, chronic inflammatory state (typically greater than 10 years) lead to sufficient SAA protein generation to cause organ injury by amyloidosis[1,2]. Amyoidosis with SAA protein is referred to as AA amyloid. Table 1 shows a list of proteins associated with amyloid formation.

Our patient showed manifestations of amyloid deposition primarily in three organ systems: the autonomic nervous system, the intestines, and the kidneys. Each of these organ involvements show the common pathology but with unique clinical findings.

***Neuropathic amyloidosis***

Amyloidosis is one of a group of several disorders that can result in neuropathy with selective involvement of the small myelinated and unmyelinated autonomic nerve fibers[3]. On a histopathologic level, amyloidosis neuropathy results from the deposition of insoluble β-fibrillar proteins within the epi-, peri-, and endoneurium as well as the perineuronal tissues and the neural vasculature. The precise pathogenesis of the associated neuropathy is not well understood, but, it is thought to be related to inflammatory, infiltrative, ischemic, and toxic-metabolic effects[4].

The earliest signs of amyloid neuropathy are usually sensory and autonomic dysfunction. Sensory symptoms usually consist of parasthesias, numbness and burning or radicular pains with earlier manifestations usually being limited to pain and temperature sensation[5]. This is because the nerve fibers responsible for pain, cold and heat are smaller in diameter than those for touch, pressure and proprioception (1-6 μm vs. 5-20 μm), thus making them more susceptible to the amyloid neuropathic process. Similarly, autonomic dysfunction is often seen in the earlier stages of the disease, as autonomic fibers are also of smaller diameter (0.4-3 μm). Alternatively, because of their larger diameter, nerve fibers for proprioception and vibratory sense are usually spared in the earlier stages of the disease[3].

Autonomic neuropathy typically occurs with primary (AL, immunoglobulin light chain) or familial (transthyretin) amyloidosis; but is not common with secondary (AA) amyloidosis. Autonomic neuropathy manifestations include gastrointestinal (diarrhea and/or constipation, vomiting, gastroparesis, and associated weight loss and malnutrition), orthostatic hypotension, genitourinary disorders (impotence, urinary incontinence, dysuria, and urinary retention), thermoregulatory, pupillomotor, and sudomotor disturbances[6].

Our patient manifested several examples of autonomic dysfunction, with the most incapacitating being chronic diarrhea and severe orthostatic hypotension which resulted in him being bedridden. The treatment of orthostatic hypotension in amyloidosis is classically a difficult one. Unfortunately, many patients do not respond to conventional treatment. Commonly used nonpharmacologic measures used to treat orthostatic hypotension include gradual positional changes when assuming the upright position; isometric counter maneuvers (which serve to decrease venous pooling and increase venous return); avoiding recumbency; compression stockings and abdominal banding (which help prevent lower extremity and splanchnic circulation pooling, respectively); increasing fluid and salt intake; and rapid ingestion of water.

Pharmacologic measures include avoiding medications which can cause orthostatic hypotension (most commonly antihypertensives, antidepressants, antiparkinsonian, and alpha-antagonist drugs), and the use of agents which can 1) help increase plasma volume, 2) increase vasoactive tone and 3) correct deficiencies within the depressed autonomic regulatory system. Drugs which increase plasma volume include fludrocortisones and desmopressin. Midodrine, pseudoepehedrine, and ephedrine are commonly used vasocontricting agents. Unfortunately, these may result in supine hypertension – an unavoidable effect which may have to be "overlooked" to accomplish the goals of symptomatic relief from orthostatic hypotension. Of note, is that Midodrine is currently the only FDA approved drug for the treatment of orthostatic hypotension. Additional agents which have shown benefit in smaller studies include high dose dexamethasone (which presumptively works by eliminating perineuronal inflammation), erythropoietin (whose benefit may be unrelated to correction of anemia, but rather due to alterations in blood viscosity and plasma volume), and pyridostigmine (which enhances sympathetic postganglionic neurotransmission by inhibiting acetylcholinesterase). Patients with amyloidosis related orthostatic hypotension often have to simultaneously adopt several of these conventional and pharmacologic measures to achieve satisfactory results[7].

Our patient was able to improve his tolerance for sitting upright on the edge of his bed by a margin of 10-15 minutes. However, his generalized weakness, deconditioning, and orthostasis prevented him from ambulating. This marginal improvement was obtained by a combination of eliminating his antidepressants with known adverse effect of orthostatic hypotension, initiating treatment with fludricortisone 0.3mg twice daily, midodrine 10mg five times daily, and strict avoidance of recumbency. He was intolerant to pyridostigmine due to severe abdominal cramping and worsening diarrhea. High dose dexamethasone in combination with his chemotherapy did not appear to provide any additional benefit. Low dose erythropoietin was tried for a short period of time but did not show any significant response and could not be continued for cost/insurance reasons. Finally, he was unable to comply with compression stockings due to exacerbation of his severe lower extremity parasthesias.

Unfortunately, amyloidosis associated with autonomic neuropathy has a poor prognosis with median survival being 13-35 months and 3-year survival of 38-50% [3]. Theoretically, with successful treatment of multiple myeloma and termination of amyloid protein formation, there may be regression of amyloid fibril neuronal deposition with resultant improvement in the associated neuropathy.

***Gastrointestinal amyloidosis***

Gastrointestinal tract involvement is very common with systemic amyloidosis but often subclinical[8]. The small intestine is the most commonly involved portion occurring in 31% of patients on autopsy studies[9]. Other portions of the tract are involved in between 10% and 20% of cases[9]. Clinically, the most common manifestations of intestinal involvement are diarrhea and malabsorption[9].

From a pathologic standpoint, the amyloid deposition occurs primarily in the blood vessels and muscular portions, often sparing the mucosa[9,10]. As the deposits build they gradually expand the highly vascular submucosa and infiltrate and replace the muscle layer. This leads to a narrowing of the intestinal lumen and altered motility. Along with this, amyloid injury to the enteric nervous system also likely plays a major role in the associated dysmotility. It should be noted that the pathologic findings varies with the underlying disease[10]. A case series comparing familial Mediterranean fever (FMF) associated amyloidosis to light chain amyloidosis showed that in FMF mucosal involvement was the norm, with muscularis involvement far less frequent and never alone; the opposite was found in light chain amyloidosis[10].

Interestingly, despite these pathologic findings, the dysmotility manifests most commonly as increased motility. Studies have shown up to a 10-fold faster rate of transit[11]. It is speculated that this may be related to amyloid-induced dysregulation in Auerbach's and Meissner's plexuses as well as the autonomic ganglia. Unfortunately, the diarrhea with amyloid is typically resistant to conventional anti-diarrheal therapy.

Less commonly, and often when amyloid deposition is secondary to underlying inflammatory bowel disease, it can present with an intermittent ileus or obstruction. Regardless of the underlying cause of the amyloidosis, this presentation carries a worse prognosis[9,12].

Our patient presented with classic symptoms with amyloid involvement of the gut: diarrhea and malabsorption. Exhaustive work-up for infectious or other etiologies was negative. As is typical of this syndrome, his symptoms did not significantly improve with anti-motility medications.

***Renal amyloidosis***

Kidney involvement with systemic amyloidosis is very common. Light chain or AL amyloidosis accounts for the majority of cases of renal amyloidosis, followed by AA. Other forms represent a very small minority of cases.[13] Regardless of the cause, non-albumin proteinuria is typically the earliest manifestation. It is important to recognize that urinalysis protein testing is sensitive almost exclusively for albumin. Although there is typically trace or mild albuminuria from the glomerular damage, detecting amyloid proteins requires total protein quantitative testing.[14] A decrease in GFR follows as deposition in glomerular and vascular structures progresses. Further work-up often reveals enlarged kidneys (although normal sized kidneys is most common), nephrotic syndrome with only mild changes in the cholesterol panel, along with manifestations of other involved organ systems.

Pathologic findings in the kidney show amyloid deposition that typically begins in the mesangium and extends into the peripheral capillaries.[15] Ultimately, involvement extends to involve the glomerular basement membrane and renal interstitium.[15] The deposits show the classic congo red staining with apple green birefringence under polarized light. Although light microscopic appearance is similar, AA and AL amyloid are easily distinguished on immunoflorescent microscopy. AA amyloid will stain strongly with antibodies to SAA protein, whereas AL

stains with antibodies to lambda light chains (or less commonly kappa).[15]

From a renal perspective our patient presented with classic findings of amyloidosis. These included moderate albuminuria and massive proteinuria, but with a normal GFR. Ultrasonography showed enlarged kidneys. Urine immunofixation revealed a monoclonal lambda protein. He also had severe edema and hypercholesterolemia that with his proteinuria gave him the nephrotic syndrome.

***Cardiac amyloidosis***

Fortunately, our patient did not yet have any evidence for cardiac amyloidosis, including no significant dysrrythmias, cardiomyopathy or congestive heart failure. He did have mild LVH on echocardiography, which may have been a harbinger for the development of cardiac amyloidosis. But at the time of his presentation there were no overt clinical signs for cardiac involvement.

***Conclusion***

Our patient presented with an unusual constellation of symptoms, but ones characteristic of systemic amyloidosis in each of the organ systems involved. His predominant symptoms were dizziness from orthostatic hypotension and diarrhea from gastrointestinal involvement. Conservative measures including compression stockings, midodrine, fludrocortisones and aggressive fluid and salt intake were implemented and enabled him to sit in a chair for a few hours at a time, but he remained unable to ambulate. He was treated with linelidomide, a thalidomide analog, along with steroids in an attempt to prevent further progression. He tolerated this well and follow-up with hematology was arranged. There was consideration for autologous stem cell transplant, however his poor performance score (ECOG 4) made him an unacceptable candidate. Sadly, despite the above treatments, he continued to deteriorate and died several months after his initial presentation to UCLA.

| Amyloid Protein | Precursor | Distribution | Type | Syndrome or Involved Tissues |
|---|---|---|---|---|
| AA | Serum amyloid A | Systemic | Acquired | Secondary amyloidosis, reactive to chronic infection or inflammation, including hereditary periodic fever (FMF, TRAPS, HIDS, FCU, and MWS) |
| AApoAI | Apolipoprotein A-I | Systemic | Hereditary | Liver, kidney, heart |
| AApoAII | Apolipoprotein A-II | Systemic | Hereditary | Kidney, heart |
| Aβ | Aβ protein precursor | Localized<br>Localized | Acquired<br>Hereditary | Sporadic Alzheimer's disease, aging<br>Prototypical hereditary cerebral amyloid angiopathy, Dutch type |
| Aβ2M | $\beta_2$-microglobulin | Systemic | Acquired | Chronic hemodialysis |
| Abri | Abri precursor | Localized or systemic | Hereditary | British familial dementia |
| Acys | Cystatin C | Systemic | Hereditary | Icelandic hereditary cerebral amyloid angiopathy |
| Afib | Fibrinogen Aα chain | Systemic | Hereditary | Kidney |
| Agel | Gelsolin | Systemic | Hereditary | Finnish hereditary amyloidosis |
| AH | Immunoglobulin heavy chain | Systemic or localized | Acquired | Primary amyloidosis, myeloma associated |
| AL | Immunoglobulin light chain | Systemic or localized | Acquired | Primary amyloidosis, myeloma associated |
| Alys | Lysozyme | Systemic | Hereditary | Kidney, liver, spleen |
| APrP | Prion protein | Localized<br>Localized | Acquired<br>Hereditary | Sporadic (iatrogenic) CJD, new variant CJD<br>Familial CJD, GSSD, FFI |
| ATTR | Transthyretin | Systemic | Hereditary<br>Acquired | Prototypical FAP<br>Senile heart, vessels |

Table 1
Classification of amyloidoses. The following proteins may also cause amyloidosis: calcitonin, islet-amyloid polypeptides, atrial natriuretic factor, prolactin, insulin, lactadherin, keratoepithelin, and Danish amyloid protein (which comes from the same gene as ABri and has an identical N-terminal sequence). CJD, Creutzfeldt-Jakob disease; FAP, familial amyloidotic polyneuropathy; FCU, familial cold urticaria; FFI, fatal familial insomnia, FMF, familial Mediterranean fever; GSSD, Gerstmann-Straussler-Scheinker disease; HIDS, hyper-IgD symdrome; MWS, Muckle-Wells syndrome; TRAPS, tumor necrosis factor receptor-associated periodic syndrome.

Adapted from:
Westermark G, Benson MD, Buxbaum JN, et al: Amyloid fibril protein nomenclature. Amyloid 2002; 9: 197-200 and Merlini G, Bellotti V: Molecular mechanisms of amyloidosis. N Engl J Med 2003; 349: 583-596.

## REFERENCES


1. **Burkitt HG, Stevens A, Lowe JS, Young, B**. "Amyloidosis" Wheater's Basic Histopathology, 3rd Edition. Churchill Livingstone, 1996. p. 56-57
2. **Merlini G, Bellotti V**. Molecular mechanisms of amyloidosis. *N Engl J Med*. 2003 Aug 7;349(6):583-96. Review. PubMed PMID: 12904524.
3. **Freeman R**. Autonomic peripheral neuropathy. *Lancet*. 2005 Apr 2-8;365(9466):1259-70. Review. PubMed PMID: 15811460.
4. **Kyle RA, Dyck PJ**. Amyloidosis and neuropathy. Peripheral neuropathy, 3rd edn. Philadelphia: WB Saunders; 1993. p. 1294-309.
5. **Adams D**. Hereditary and acquired amyloid neuropathies. *J Neurol*. 2001 Aug;248(8):647-57. Review. PubMed PMID: 11569892.
6. **Kelly JJ Jr, Kyle RA, O'Brien PC, Dyck PJ**. The natural history of peripheral neuropathy in primary systemic amyloidosis. *Ann Neurol*. 1979 Jul;6(1):1-7. PubMed PMID: 228587.
7. **Freeman R**. Clinical practice. Neurogenic orthostatic hypotension. *N Engl J Med*. 2008 Feb 7;358(6):615-24. Review. PubMed PMID: 18256396.
8. **Sattianayagam PT, Hawkins PN, Gillmore JD**. Systemic amyloidosis and the gastrointestinal tract. *Nat Rev Gastroenterol Hepatol*. 2009 Oct;6(10):608-17. Epub 2009 Sep 1. Review. PubMed PMID: 19724253.
9. **Ebert EC, Nagar M**. Gastrointestinal manifestations of amyloidosis. *Am J Gastroenterol*. 2008 Mar;103(3):776-87. Epub 2007 Dec 12. Review. PubMed PMID:18076735.

10. **Gilat T, Revach M, Sohar E**. Deposition of amyloid in the gastrointestinal tract. *Gut.* 1969 Feb;10(2):98-104. PubMed PMID: 5766053; PubMed Central PMCID:PMC1552807.
11. Guirl MJ, Högenauer C, Santa Ana CA, Porter JL, Little KH, Stone MJ, Fordtran JS. Rapid intestinal transit as a primary cause of severe chronic diarrhea in patients with amyloidosis. Am J Gastroenterol. 2003 Oct;98(10):2219-25. PubMed PMID: 14572571.
12. Tada S, Iida M, Yao T, Kitamoto T, Yao T, Fujishima M. Intestinal pseudo-obstruction in patients with amyloidosis: clinicopathologic differences between chemical types of amyloid protein. Gut. 1993 Oct;34(10):1412-7. PubMed PMID: 8244111; PubMed Central PMCID: PMC1374552.
13. Schwimmer JA, Joseph RE, Appel GB. Amyloid, fibrillary, and the glomerular deposition diseases in therapy. In: Wilcox CS, Brady HR, editors. Nephrology and Hypertension. Philadelphia: Saunders; 2003. p. 253-61.
14. Fogazzi GB, Pirovano B. Urinalysis. In: Frehally J, Floege J, Johnson RJ, editors. Comprehensive Clinical Nephrology, 3rd edition. Philadelphia: Mosby Elsevier; 2007. p. 36-7.
15. Appel GB, Radhakrishnan J, D'Agati V. Secondary Glomerular Disease – Amyloidosis. In: Brenner BM, Levine SA, editors. Brenner and Rector's The Kidney, 8th edition. Philadelphia: Saunders; 2007. p. 1101-4.

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