

# Cryoglobulinemic neuropathy: a treatable cause of polyneuropathy

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## Abstract

We report a case of a 62 year-old woman who presented with progressive, asymmetric dysesthesias over 1 year. She was previously diagnosed with idiopathic neuropathy and sought a second opinion. Electrodiagnostic studies revealed an asymmetric, sensory neuropathy. Laboratory studies revealed cryoglobulinemia associated with hepatitis C infection. She underwent treatment with ribavirin and interferon (Gilead Sciences). Her hepatitis studies were undetectable and her neuropathic symptoms resolved. We review the presentation of cryoglobulinemic neuropathy. Emphasis is placed on considering this treatable cause of neuropathy, which may be under-recognized.

**Keywords:** Neuropathy, cryoglobulins, peripheral nervous system

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## INTRODUCTION

Peripheral neuropathy (PN) is a common condition, with a prevalence of up to 8% of patients over age 55 (1). There are myriad etiologies which may lead to PN (1). After extensive investigations at tertiary centers, up to 25% may still be considered cryptogenic or idiopathic (2, 3). We report the case of a treatable cause of acquired neuropathy, initially considered idiopathic. Cryoglobulinemic neuropathy associated with hepatitis C may be an under-recognized cause of cryptogenic neuropathy (4, 5). We review salient features of the presentation, diagnostic studies, treatment and outcomes.

## CASE PRESENTATION

Verbal informed consent was obtained from the patient in this report. A 62-year-old healthcare worker reported 1 year of numbness and tingling that progressed asymmetrically from her feet to the left knee and up to the right ankle. She also noticed dysesthesias in both hands and tongue numbness. Additionally, she reported generalized fatigue and malaise. This led to a sedentary lifestyle. Based on prior evaluations, she was diagnosed with idiopathic polyneuropathy.

She denied intravenous drug use, tattoos or sexual history with multiple partners. She denied recent accidental needle sticks. There were no recently administered medications or toxin exposures.

Neurologic examination showed normal cranial nerves, reflexes and strength. Sensory examination revealed decreased proprioception and vibration at both toes. Romberg's sign was positive. Sensation was reduced to all modalities from the left knee to the foot and from the right ankle to the foot. Sensory examination was normal subjectively to all modalities in the hands despite symptoms.

There were no findings suggestive of hereditary neuropathy, such as pes cavus, pes planus or family history. Therefore, laboratory and electrodiagnostic investigations were repeated to assess for an acquired etiology to account for the asymmetric features and subacute progression.

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Prior laboratory studies showed normal thyroid function tests, vitamin B6, vitamin B12, erythrocyte sedimentation rate, complete blood count with differential and comprehensive metabolic panel. Magnetic resonance imaging (MRI) of the brain without contrast was unremarkable. MRI cervical spine without contrast showed incidental findings of mild disc degeneration and C4-5 and C6-7 without cord signal abnormalities or significant neuroforaminal stenoses.

Electrodiagnostic studies were then performed. These studies showed a non-length-dependent, sensory neuropathy with asymmetric features.

Other studies including paraneoplastic antibodies, vitamin B1, antinuclear antibody and serum immunofixation were unremarkable. Due to a prior history of tobacco use, chest computed tomography without contrast was performed and did not reveal any mass or lymphadenopathy. She subsequently underwent routine malignancy screenings for her age, mammography and colonoscopy, which were normal.

Due to her occupation, hepatitis panel was also evaluated. Hepatitis C was positive with a high titer on polymerase chain reaction. Serology showed elevated cryocrit with positive rheumatoid factor. Transaminase levels and comprehensive metabolic panel were unremarkable. The patient had no clinical signs of cirrhosis.

The patient was referred to a gastroenterologist for new diagnosis of hepatitis C. She was diagnosed with cryoglobulinemic vasculitic neuropathy. She was started on standard treatment for hepatitis C, ribavirin and interferon (Gilead Sciences, Foster City, United States) (6-8).

Her neuropathic symptoms completely abated on hepatitis treatment. Her cryocrit levels were significantly reduced on follow up serologic testing. Her fatigue and malaise also resolved.

## DISCUSSION

After extensive investigations, up to 25% of polyneuropathies are considered idiopathic or cryptogenic (2, 3). However, this population of patients often had chronic (>60 months), symmetric, sensory symptoms (3). We report a patient who had subacute, progressive, asymmetric sensory symptoms. Hepatitis C studies were obtained and confirmed the new diagnosis of hepatitis C with associated cryoglobulinemia.

Hepatitis C is prevalent in 2% of the US population, but could be up to 22% in other regions of the world, such as Egypt (9). Neuropathy is the most common extrahepatic manifestation of hepatitis C, estimated at 10-15% prevalence of all hepatitis C cases (10). Cryoglobulinemic vasculitis is considered the primary etiology of the neuropathy (11). Cryoglobulins (which may be asymptomatic) are found in up to 44% of patients with

hepatitis C (11). Cryoglobulins are immune complexes which precipitate at temperatures less than 37 degrees Celsius (11). The type of cryoglobulinemia is determined by the make up of the immunoglobulin (Ig) complexes. Type 1 cryoglobulinemia is considered part of a lymphoproliferative disorder with a monoclonal IgM. Type 2 cryoglobulinemia complexes are made up of monoclonal IgG and IgM complexes. Type 3 cryoglobulinemia consists of polyclonal IgG and IgM complexes. Cryoglobulin complexes likely deposit into blood vessels of the vasa nervorum, leading to an inflammatory reaction. Nerve biopsies performed in patients with cryoglobulinemic neuropathy reveal microvasculitis of small arteries. Electron microscopy of these nerves reveal proteinaceous deposition in vessel walls, which are likely cryoprecipitate (11).

In a retrospective review of undetermined peripheral neuropathies in Southern Europe, cryoglobulinemic neuropathy was considered to be the most common acquired etiology of neuropathy determined in up to 11% of patients (5, 12). This differed from prior retrospective review of idiopathic neuropathy, but the authors propose this may be due to the higher prevalence of hepatitis C in the European region (2, 3). The American Academy of Neurology practice parameter currently considers vitamin B12 testing, serum immunofixation and glucose testing to be the most high yield serological tests (4). Thoughtful history and physical examination are recommended by several groups to help determine the extent of further testing (2, 3). Our patient had a similar phenotype to the other cryoglobulinemic neuropathy patients. Salient features of cryoglobulinemic neuropathy included mean age of presentation 46 to 75 years, female predominance and mostly asymmetric sensory neuropathy characterized by dysesthesias. Purpura was present in 7 of 11 patients, but 4 of 11 patients did not have purpura, such as our patient (5, 12, 13).

The initial treatment for cryoglobulinemic neuropathy is often interferon and ribavirin (10). However, there are case reports of patients' neuropathy worsening or not responding to these treatments (10). There are a few randomized controlled trials of rituximab treatment in neuropathy. However, they have been criticized for lack of electrodiagnostic data, objective and subjective neuropathic outcomes (10). Intravenous immunoglobulin and plasma exchange have been reported to cause improvement, but not in randomized controlled trials (10).

## CONCLUSION

As our patient's symptoms resolved completely with treatment for hepatitis C, we want to emphasize the importance of considering cryoglobulinemic neuropathy in patients with atypical features for an idiopathic sensory neuropathy.

**Informed Consent:** Verbal consent was obtained by the patient who participated in this study.

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