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Amyloid-like IgM deposition neuropathy: a distinct clinico-pathologic and proteomic profile disorder

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Abstract

Some patients with immunoglobulin paraproteinemic neuropathy have intra-nerve deposits that morphologically mimic amyloid, but do not stain with Congo red. Patients with amyloid-like deposits were identified. The nerve amyloid-like aggregates were studied by laser microdissection and dual mass spectrometry. Three male patients, all with IgM gammopathy, and neuropathy were identified. Follow-up, disease duration was 5, 19, and 7 years, respectively. All had progressive asymmetric sensory-onset distal axonal polyneuropathy with late motor involvement. Autonomic symptoms occurred in only one after 13 years of symptoms. None had clinical cardio-renal involvement. One had skin papules with dermal amyloid-like deposits. Endoneurial amyloid-like deposits had granulo-fibrillar ultrastructure. Mass spectrometry of laser-dissected deposits identified IgM pentameric macroglobulin (heavy, light, and joining chains) without amyloid-associated proteins including absent apolipoprotein E and serum amyloid P-component. Amyloid-like neuropathy has distinct clinical, pathologic, and proteomic features which expand the spectrum of IgM neuropathies. Patients have favorable survival, relative absence of autonomic features, and distinct proteomic profiles of the infiltrative protein in nerve.

Keywords

amyloid; IgM; mass spectrometry; neuropathy

Introduction

The range of paraproteinemic neuropathies is diverse, with varied immune and infiltrative mechanisms. Among the immune varieties, IgM is particularly highlighted with painless symmetric sensory ataxia. In the infiltrative varieties (IgM, IgG, IgA), monoclonal immunoglobulin light chains can deposit in nerve tissue as amyloid with distinctive histologic characteristics: (1) Congo red birefringence under polarized light and (2) crisscrossing fibrils of 8–10 nm in diameter under electron microscopy (Glennner, 1980). Amyloid associated proteins, that is, serum amyloid P-component (SAP) and apolipoprotein E (ApoE), are universally present within amyloid aggregates (Gallo et al., 1988; Buxbaum et al., 1990; Pepys et al., 1994; Klein et al., 2010). Patients with systemic AL amyloidosis have uniformly poor prognosis with fatality related to cardiac and renal involvements. AL

amyloidosis neuropathy is typically axonal, motor and sensory, length dependent with prominent autonomic failure including orthostasis, anhidrosis, erectile dysfunction, and gastrointestinal dysmotility (Rajkumar et al., 1998).

Paraproteins can also deposit in nerve as amyloid-like aggregates with similar morphology to amyloid but not staining with Congo red and not showing the distinctive fibrillar ultrastructure, ranging from small amounts detectable by electron microscopy (Vallat et al., 1980; 1995; Sherman et al., 1983; Meier et al., 1984; Vital and Vital, 1993; Vital et al., 1982; 1985; 1991; 2001) to extensive deposits evident on light microscopy (Darnley, 1962; Iwashita et al., 1974; Carrier et al., 1978; Lamarca et al., 1987; Yee et al., 1989; Moorhouse et al., 1992; Vallat et al., 2008a; Leschziner et al., 2009; Luigetti et al., 2010). Western blot, immunostaining, and immunoelectron microscopy of amyloid-like nerve deposits in IgM neuropathy patients have demonstrated both heavy (IgM mu) and light chain (kappa or lambda) composition (Yee et al., 1989; Vallat et al., 2008a; Leschziner et al., 2009). Although those earlier descriptions outline the occurrence of neuropathy, longitudinal follow-up and clinical descriptions are limited (Yee et al., 1989; Vallat et al., 2008a; Leschziner et al., 2009).

There have been recent advancements in the proteomic evaluation of nerve amyloid by laser micro dissection (LMD) liquid chromatography dual mass spectrometry (LC-MS/MS) (Klein et al., 2010). Determination of amyloid type is possible independent of clinical information. This technical advancement also allows for molecular classification of proteins including those associated with amyloid fibrils such as SAP and ApoE and details of the immunoglobulin proteins. Herein we describe the mass spectrometry protein profile of identified patients. We characterize the clinical phenotypes and identify the protein composition of these deposits using mass spectrometry approach.

Patients and Methods

Patients

After Institutional Review Board approval, we searched the electronic database of the Mayo Clinic Peripheral Nerve Laboratory, Rochester, MN, for nerve biopsy cases evaluated from 1980 to 2010. The word “amyloid” was specifically queried and those with “Congo-negative” or “amyloid-like” were targeted for review. Pathologic findings of all available nerve biopsy slides identified as potentially having amyloid-like deposits were reviewed. An amyloid-like deposit was defined as a relatively extensive extracellular aggregate readily seen on light microscopy with the same morphological properties of amyloid but not staining with Congo red. Clinical information was obtained from medical records, including history, laboratory results, and electrophysiology and if available, autonomic studies evaluating adrenergic, cardiovagal and sudomotor functions. The severity and distribution of autonomic deficits were quantitated with the Composite Autonomic Severity Score (CASS), a validated instrument normalized for age and gender, which ranges from 0 (no autonomic deficits) to 10 (severe widespread dysautonomia) (Low, 1993).

Nerve biopsy

Identified biopsy specimens had been processed under standard techniques for preparation of teased fibers, paraffin, epoxy sections, and electron microscopy (Dyck et al., 1993). Congo red and methyl violet stains were used for amyloid detection. Immunohistochemistry evaluation performed in all cases included antibodies to SAP, ApoE, pre-albumin (transthyretin), kappa, and lambda.

Mass spectrometry based proteomic analysis

The specific methodology has been published in detail previously (Rodriguez et al., 2008; Vrana et al., 2009; Klein et al., 2010). The Congo red-negative nerve deposits were identified on paraffin section under light microscopy and resected by laser microdissection. To characterize the protein composition of these deposits, the microdissected fragment was digested by trypsin generating peptide fragments that were analyzed by nanoflow liquid chromatography electro-spray tandem mass spectrometry (MS). MS raw data files were queried using three different algorithms (Mascot, Sequest and X!Tandem), the results were assigned peptide and protein probability scores and displayed using Scaffold (Proteome Software, Portland, OR, USA). For each case, a list of proteins based on peptides identified by MS was generated (Swiss Protein Database, 2010).

Results

Patients

Three men (ages at onset: 60, 61, and 70 years) were identified. Two were seen at our institution. The third patient's nerve biopsy was processed and interpreted at our laboratory and had available outside records. Time from symptom onset to nerve biopsy ranged from 4 to 11 years. Shared core clinical features (detailed below) were: (1) IgM lambda monoclonal gammopathy without evidence for amyloid; (2) progressive asymmetric, sensory-onset, late motor distal axonal confluent neuropathy without significant dysautonomia; (3) disease confinement to nerves (plus skin in one) despite 5–19 years of disease.

Case 1—A 62-year-old man was referred to our institution having 2 years of distal painful sensory disturbances and 1 year of distal weakness. He initially noticed “asleep” numbness and tingling in his left heel that progressed to his ankle over 2 months, followed by right heel involvement. Symptoms then reached bilateral mid-shin level at 3 months. The left fingers then became involved with progression to right fingers over weeks. At 5 months his neurologic examination revealed asymmetric distal sensory loss and an IgM lambda monoclonal protein (IgM > 2 mg/dl) with anti-MAG reactivity (titer = 1 : 1,600). A diagnosis of Waldenström's macroglobulinemia was established by bone marrow biopsy. Painful sensory disturbances worsened despite several weeks of prednisone (40 mg daily) and mycophenolate mofetil (1,000 mg daily). At 9 months he was clinically diagnosed with inflammatory multiple mononeuropathy and given high doses of prednisone (90 mg daily) and four weekly infusions of rituximab (375 mg/m²). He still progressed and at 1 year sensory disturbances had become symmetric to his wrist and shins with now new distal ankle (dorsiflexion, plantar flexion) asymmetric limb weakness, which continued to worsen.

Repeat bone marrow studies confirmed a diagnosis of Waldenström's macroglobulinemia (M spike=1.9 g/dl, serum IgM, 2.81 g/dl). Electrophysiology showed: (1) widespread loss of sensory responses (sural, median, ulnar, radial); (2) loss of motor responses in legs (peroneal, tibial, ulnar [0.6, normal 4 ms]) without conduction slowing, and (3) reduced recruitment of large motor units plus fibrillations in a distal predominant pattern. Chemotherapy with alkylating agents was recommended but not given by the local physician. After 5 years of illness the patient became confined to a wheelchair with severe pain (requiring opioids), sensory ataxia, hand amyotrophy, and foot drop. He had no autonomic complaints at last follow-up. However, autonomic testing performed at 4 and 5 years showed subclinical abnormalities that were minimal with limited progression (CASS 2 to CASS 4 over a 1-year period) involving postganglionic sudomotor and cardiovagal autonomic fibers with sparing adrenergic function. CSF studies and cauda equina neuroimaging were unrevealing. There was no evidence of systemic involvement (normal

cardiac, renal, and body imaging studies; Congo red negative fat aspirate and bone marrow). A sural nerve biopsy was performed 4 years after symptom onset (Figs. 1 and 3).

Case 2—A 68-year-old man presented to our institution with an 8-year history of sensory symptoms and a 1-year history of weakness affecting distal limbs without autonomic complaints. He first experienced gradual pain, paresthesias and loss of feeling ascending from left toes to ankle over 2 years followed by contralateral progression from right toes to ankle over 2 more years. Aside from sensory symptoms, he felt well. Deep and sharp pains worsened leading him to seek medical treatment. By 6 years, right fingers became involved, a nail piercing through his heel was painless (analgesia of soles) and nodular papules appeared in distal lower limb skin. By 7 years, symptoms spread to his left fingers. Besides distal sensory loss, an evaluation elsewhere revealed palpable enlarged superficial cutaneous nerves and skin papules (Fig. 2) in distal legs with asymmetric thenar atrophy. Nerve conductions and needle EMG showed severe, chronic sensory, early motor, asymmetric distal axonal neuropathy with absent sensory responses and decreased motor responses in lower limbs without fibrillations or motor unit abnormalities.

An IgM lambda monoclonal gammopathy of unknown significance (M spike = 2.24 g/dl; serum IgM = 2.77 g/dl) was confirmed by serial bone marrow studies. Repeat electrophysiology at 8 years showed marked interval progression with: (1) widespread loss of sensory responses; (2) loss of motor responses in lower extremities with severely reduced median but normal ulnar motor responses; and (3) reduced recruitment of large motor unit potentials with fibrillations potentials with distal predominance. Treatment with chlorambucil was considered but never given due to recurrent bronchopneumonias. At 11 years, six rounds of plasma exchange had no effect on his neuropathy.

At 13 years follow-up he had disabling distal pain, severe sensory ataxia, asymmetric foot drop requiring orthotics and amyotrophic hands without autonomic manifestations. During the next 6 years he developed painless foot ulcers and became walker-dependent with multiple falls. Later, slowly progressive orthostatic hypotension ensued with autonomic laboratory evidence of interval progression over several years late in the disease from mild subclinical loss of distal postganglionic sudomotor fibers (CASS = 2) to a generalized autonomic failure (CASS = 8) involving post-ganglionic sudomotor, cardiovagal, and adrenergic fibers. At 18 years his total Neuropathy Impairment Score was 84, reflecting a severe diffuse neuropathy. The patient expired after 19 years of disease at age 74 from unrelated pneumonia.

Throughout his disease, repeat bone marrow studies showed non-progressive slight plasmacytosis. During the last 8 years of disease his serum M-spike levels ranged from 0.91 to 2.4 g/dl (median = 1.96 g/dl) and his serum IgM levels from 496 to 2770 mg/dl (median = 1432 mg/dl). He developed no anemia, hepatosplenomegaly, or lymphadenopathy. Although his weight remained relatively stable early in the disease, he had a gradual 20-lb weight loss over the last 6 years. Cardiac and renal function remained normal. Congo red stain on bone marrow, enlarged hilar lymph nodes, alveolar and rectal tissues were negative for amyloid. At autopsy, the heart, kidney, liver, spleen, and lung showed no features of amyloidosis or immunoglobulin deposition disease. Distal sensory cutaneous nerve biopsy was obtained at 10 and 11 years from symptom onset (Fig. 2). Biopsies of skin papules were performed at 11 years and at autopsy (Fig. 2).

Case 3—A 77-year-old man presented to an outside institution with a 7-year history of a gradual and mildly asymmetric sensory disturbances and a 2-year history of weakness involving distal limbs. He developed numbness and tingling that started at the toes. The paresthesias gradually became painful. Over the next years symptoms spread to involve both

feet and eventually to just below the knees. At 4 years, sensory symptoms had reached his hands that gradually spread to wrists at presentation. At 5 years, gradual weakness and atrophy of distal limbs ensued. IgM lambda Waldenström's macroglobulinemia was confirmed by bone marrow studies. At 7 years, he had disabling pain (requiring opioids), severe sensory loss (small fiber-predominant), unilateral foot drop and bilateral hand amyotrophy with claw deformities. Electrophysiology was reportedly consistent with distal sensory motor axonal damage. There was no clinical evidence of autonomic or systemic organ involvement at 7 years. A sural nerve biopsy was performed 7 years after symptom onset.

Nerve biopsy studies

Sural (cases 1 and 3) and superficial peroneal (case 2) nerve biopsies were analyzed. Similar histopathological, immunohistochemical, and ultrastructural features were found. There were no lymphomatous infiltrates. Teased fibers and semithin sections revealed a severe reduction or absence of large and small myelinated nerve fibers with axonal degeneration as the predominant pathologic alteration. In those with residual nerve fibers, the loss was multifocal between nerve fascicles (Fig. 1). There was large amorphous, amyloid-like material in the endoneurium surrounding mainly endoneurial microvessels and subperineurial spaces, but also extending into the interstitial space at times infiltrating and replacing most of the endoneurium with resultant disruption of its architecture (Figs. 1–3). No deposits were seen in the epineurium. The deposits were eosinophilic and strongly positive on periodic acid-Schiff (PAS) staining (Fig. 1). These aggregates were morphologically indistinguishable from amyloid (amorphous, acellular, homogeneous), but lacked its tinctorial (negative on Congo red stain under polarized and rhodamine optics; and on methyl violet stain) (Figs. 1–3) and immunohistochemical (SAP and ApoE negative) characteristics. Immunohistochemical battery for amyloid protein subtyping showed no reactivity to mu heavy chain, lambda light chain, kappa light chain, amyloid A protein, and pre-albumin (transthyretin). Nerve specimens known to have amyloid deposits were tested as controls and all showed congophilia.

Electron microscopy of endoneurial perivascular deposits revealed small fields of randomly arranged, non-branching fibrils of 9–10 nm in diameter, indistinguishable from amyloid fibrils but associated with abundant granular material suggesting a granulofibrillar ultrastructure (Fig. 1). Case 1 had epineurial inflammation characterized by polyclonal (CD45, CD3, and CD20 positive) small, moderate, and large perivascular lymphocytic infiltrations that at times involved and disrupted vessel walls with neovascularization and hemosiderin deposition. These findings suggested microvessel wall inflammation with resultant ischemia (Fig. 3). Case 2 had a lesser degree of epineurial inflammation which also showed occasional vessel wall disruption by inflammatory cells associated with multifocal fiber loss and perineurial thickening (Fig. 2). Case 3 showed no superimposed epineurial inflammation.

Mass spectrometry results

In all cases, MS of the microdissected tissue detected a peptide profile that was consistent with the whole IgM lambda immunoglobulin molecule (pentameric macroglobulin) based on the detection of immunoglobulin mu heavy chain constant region, immunoglobulin lambda light chain constant region and immunoglobulin J chain. There was no evidence of SAP and ApoE in the LC-MS/MS analysis.

Discussion

In the consideration of the relation of a discovered monoclonal protein's relevance to an identified neuropathy, the specific clinical features are helpful. Painful asymmetric onset sensory neuropathy was the associated phenotype in those with IgM nerve deposition disease. These features are collectively distinct from described immune mediated IgM disease, that is, IgM-MGUS or Waldenström's neuropathy (Klein et al., 2011) and from amyloidosis neuropathy (Dyck et al., 1986). Proteomic analysis of three separate patients revealed that the amyloid-like material was composed of μ -heavy chain, λ -light chain and J-joining chain without SAP and ApoE, suggesting deposition of the whole IgM pentameric molecule (macroglobulin) without amyloid-associated proteins. The strong PAS-positivity of deposits suggested a very high carbohydrate content as seen in macroglobulins (Heimbürger et al., 1964). Although some fibrils similar to amyloid were seen on electron microscopy, the predominant ultrastructure was granulofibrillar.

Affected persons had a lower more than upper limb, asymmetric sensory more than motor, distal axonal polyneuropathy with prominent painful sensory disturbances. Also present was stepwise progression; late distal amyotrophy after prolonged pure sensory involvement; absent autonomic complaints at evaluation and nadir; absent systemic organ involvement, apart from unique skin involvement in one. A more favorable long-term survival compared to amyloid and severe morbidity with disability due to severe pain; loss of hand function (variable sensory ataxia plus weakness); and gait impairment (variable sensory ataxia plus foot drop). In addition to support a shared clinical phenotype reported at presentation (Darnley, 1962; Iwashita et al., 1974; Lamarca et al., 1987; Yee et al., 1989; Moorhouse et al., 1992; Vallat et al., 2008a; Leschziner et al., 2009; Luigetti et al., 2010), we provide more extensive studies, longer somatic and autonomic follow-up, with quantification of generally spared autonomic deficits and confirmation of lack of other organ involvements by pathology and autopsy.

The identified clinical, ultrastructural and proteomic features argue against amyloid pathology as the aggregate component of amyloid-like deposits in our three patients: (1) no autonomic complaints long after disability onset; (2) no major systemic organ involvement; (3) a much more favorable long term survival (up to 13 years); (4) a granulofibrillar aggregate ultrastructure; and (5) a unique aggregate proteomic profile (IgM pentameric macroglobulin without amyloid-associated proteins).

In our patients, the massive nerve deposits were restricted to the endoneurium with a multifocal or diffuse deposition distribution, localizing to the perivascular, interstitial and subperineurial spaces. Endoneurial aggregates were confined by the perineurium without evidence of epineurial involvement. Prior reports have emphasized the same nerve distribution (Darnley, 1962; Iwashita et al., 1974; Lamarca et al., 1987; Yee et al., 1989; Moorhouse et al., 1992; Vallat et al., 2008b; Leschziner et al., 2009; Luigetti et al., 2010). The mechanisms of deposition and endoneurial selectivity remain unknown. Endoneurial connective tissue autoantibody activity has been proposed (Sherman et al., 1983; Yee et al., 1989).

The mechanism of nerve fiber alteration, that is, axonal degeneration, in both amyloid and our amyloid-like disease remains unknown. Mechanical compression and microcirculation alterations with tissue hypoxia have been proposed in IgM deposition neuropathy (Yee et al., 1989). In addition to the IgM deposition seen, there was epineurial perivascular and vascular inflammation with vessel wall disruption seen in two of our cases. An inflammatory component of IgM deposition pathogenesis may be suggested, including possibly of microvasculitis potentially resulting in ischemia, contributing to nerve fiber loss and to the

asymmetric and painful manifestations. Moreover, the much larger epineurial perivascular and vascular inflammatory involvement in case 1 (Fig. 3) may have also contributed to the more subacute progression compared to the more gradual course of cases 2 and 3 with lesser or no epineurial inflammation. Modest epineurial perivascular inflammation has previously been reported in amyloid-like IgM neuropathy (Iwashita et al., 1974; Lamarca et al., 1987). The mechanism of predominant somatic fiber selectivity, including cfibers, with relative sparing of autonomic involvement remains unknown.

Immunomodulating therapies aimed at reducing inflammation or macroglobulin production may not allow for improvement at presentation if axonal degeneration and endoneurial architecture destruction is too advanced. Nerve biopsies performed after several years of disease in our patients delayed mechanism-specific treatments. Whether small endoneurial paraprotein aggregation detectable only by electron microscopy or immunofluorescence (Vallat et al., 1980; 1995; Dalakas and Engel, 1981; Vital et al., 1982; 1985; 1991; 2001; Sherman et al., 1983; Meier et al., 1984; Vital and Vital, 1993) represents an earlier stage of amyloid-like neuropathy, hence the therapeutic window of opportunity, or a separate disease entity remains to be elucidated.

IgM amyloid-like neuropathy results from whole IgM-molecule deposition into nerve without amyloid associated proteins. The clinical and histopathologic features distinguish it from other paraprotein associated neuropathies and expand the spectrum of IgM associated neuropathies. As nerve biopsy is the only way to recognize such a mechanism, it should be considered early in severe progressive IgM paraproteinemic neuropathy, even with positive anti-MAG serology and with absence of systemic involvement, as early treatment designed to reduce circulating IgM proteins is theorized as potentially beneficial, but large treatment trials may be prohibitive among persons with such a rare condition.

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Figure 1.

Pathologic and ultrastructural features of amyloid-like nerve deposits. (Case 1, left column; case 3, right column). Case 1 (A, C, E, and G): serial transverse paraffin sections of one nerve fascicle of sural nerve (A and C) show infiltrating homogeneous material in the central endoneurial region (arrows bordering deposit) that is eosinophilic on H&E stain (A) but does not stain with Congo red (C). On Luxol Fast Blue/Periodic Acid-Schiff (PAS) stain of a different nerve fascicle (E) the infiltrating homogeneous material is surrounding endoneurial blood vessels (arrows) and subperineurial space (arrowhead). Electron microscopy of these deposits (G) reveals a few fibrils indistinguishable from amyloid (6–9 nm wide; black asterisk) imbedded in abundant granular material (white asterisk) consistent with a granulo-fibrillar ultrastructure. Case 3 (B, D, F, and H): transverse semithin epoxy section stained with methylene blue (B) taken from superficial peroneal nerve demonstrates a nerve fascicle with severe loss of nerve fibers and thick infiltrating homogenous material (arrow) surrounding endoneurial blood vessels. Serial transverse paraffin sections (D and F) show that endoneurial perivascular (arrow) and subperineurial (arrowhead) deposits lack congophilic apple-birefringence under polarized light (D) and show strong PAS positivity (F). Electron microscopy of these deposits (H) reveals abundant amorphous material with granular appearance (white arrow) and some fibrils (black asterisk) similar to amyloid (6–9 nm wide).

Figure 2.

Amyloid-like deposits in nerve and skin. Case 2: transverse paraffin section of sural nerve stained with Congo red (A) reveals marked infiltration of homogeneous material around all the subperineurial space (arrows) lacking congophilia. Transverse semithin epoxy section stained with methylene blue (B) shows multifocal fiber loss between fascicles 1 (moderate) and 2 (severe). Note the marked thickening of the perineurium of fascicle 2 (black asterisk). High magnification of an epineurial arteriole stained with Luxol Fast Blue/PAS on a transverse paraffin section (C) reveals a moderate perivascular inflammatory infiltrate with involvement of vessel wall. The nodular papules (D) seen on the skin of the left foot contained Congo-red negative amyloid-like material in the dermis.

Figure 3.

Epineurial perivascular inflammatory infiltrate with vessel wall involvement. Case 1: Transverse paraffin sections of sural nerve focusing on coexisting epineurial changes. H&E stain (A) shows a large epineurial inflammatory infiltrate with vessel wall involvement. Immunohistochemistry reveals that the mononuclear inflammatory cells are LCA-positive (B) lymphocytes containing both CD-3 positive (C) T and CD20-positive (D) B-cell populations, consistent with a polyclonal inflammatory process and not with a malignant lymphocytic infiltration. Turnbull blue staining (E) shows hemosiderin deposition in one epineurial microvessel with perivascular inflammation, suggesting old vessel wall damage with bleeding. Smactin (F) reveals a small perivascular inflammatory cell infiltrate of mononuclear cells that separate muscle fiber layers of a microvessel wall. Altogether, these findings suggest that an inflammatory process, possibly microvasculitis, can accompany an amyloid-like neuropathic process.