Clinical Case Report

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Magnetic resonance imaging of the spinal cord in the evaluation of 3 patients with sensory neuronopathies: Diagnostic assessment, indications of treatment response, and impact of autoimmunity

A case report

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Abstract

Rationale: Sensory neuronopathy can be a devastating peripheral nervous system disorder. Profound loss in joint position is associated with sensory ataxia, and reflects degeneration of large-sized dorsal root ganglia. Prompt recognition of sensory neuronopathies may constitute a therapeutic window to intervene before there are irreversible deficits. However, nerve-conduction studies may be unrevealing early in the disease course. In such cases, the appearance of dorsal column lesions on spinal-cord MRI can help in the diagnosis. However, most studies have not defined whether such dorsal column lesions may occur within earlier as well as chronic stages of sensory neuronopathies, and whether serial MRI studies can be used to help assess treatment efficacy. In this case-series of three sensory neuronopathy patients, we report clinical characteristics, immunological markers, nerve-conduction and skin-biopsy studies, and neuroimaging features.

Patient concerns: All three patients presented with characteristic features of sensory neuronopathy with abnormal spinal-cord MRI studies. Radiographic findings included non-enhancing lesions in the dorsal columns that were longitudinally extensive (spanning ≥ 3 vertebral segments).

Diagnoses: All patients had anti-Ro/SS-A and/or anti-La/SS-B antibodies, with patients one and two having Sjögren's syndrome. MRI findings were similar when performed in the earlier stages of a sensory neuronopathy (patient one, after four months) and chronic stages (patients two and three, after five and three years, respectively).

Interventions: Patient one was treated with rituximab combined with intravenous immunoglobulin therapy.

Outcomes: Patient one was initially wheelchair-bound and had improved ambulation after treatment. In this patient, serial MRI studies revealed partial resolution of dorsal column lesions, associated with decreased sensory ataxia and improved nerve-conduction studies.

Lessons: In addition to vitamin B12 and copper deficiency, it is important to include sensory neuronopathies in the differential diagnosis of dorsal column lesions. MRI spinal-cord lesions have similar appearances in the earlier as well as chronic phases of a sensory neuronopathy, and therefore suggest that such dorsal column lesions may reflect inflammatory as well as a gliotic burden of injury. MRI may also be a useful longitudinal indicator of treatment response.

Abbreviations: ACR/EULAR = American College of Rheumatology/European League Against Rheumatism, DRG = dorsal root ganglia, IVIg = intravenous immunoglobulin, MRI = magnetic resonance imaging, PNS = peripheral nervous system, RF = rheumatoid factor, SNAPs = sensory nerve action potentials, SS = Sjögren syndrome.

Keywords: auto antibodies, sensory ganglionopathies, sensory neuronopathies, Sjögren syndrome, small-fiber neuropathies, spinal-cord lesions

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1. Introduction

Sensory neuronopathy is a devastating peripheral nervous system (PNS) disorder that may present with loss of joint position, severe sensory ataxia, pseudo-athetotic movements, and can even relegate patients to wheelchairs when there is preserved strength.[1–7] The sensory neuronopathies may complicate a wide spectrum of diseases evaluated by different medical specialists, which include rheumatologists (sensory neuronopathies associated with Sjögren syndrome [SS] and systemic lupus erythematosus), gastroenterologists (associated with celiac disease and autoimmune hepatitis), hematologists and oncologists (associated with monoclonal gammopathies and paraneoplastic syndromes), pulmonologists (associated with sarcoidosis), and family medicine practitioners and internists (caring for systemic manifestations of these disorders).[1–7] There may only be a limited therapeutic window to intervene before patients may suffer from irreversible deficits. Therefore, diagnostic strategies that can detect sensory neuronopathies in their earliest and most inaugural stages are essential.

Spinal-cord magnetic resonance imaging (MRI) studies are traditionally regarded as a diagnostic modality to detect central nervous system causes of a myelopathy, and are not typically used in the evaluation of PNS disorders.[8] However, it may be underappreciated that spinal-cord lesions which affect the dorsal column can be detected in patients with sensory neuronopathies.[1] In such cases, dorsal column lesions result from the degeneration of the central afferent tracts between the dorsal root ganglia (DRG) and its synapse at the dorsal-horn. Such lesions may also be "longitudinally extensive," defined as spanning ≥ 3 vertebral segments. However, neuroradiology textbooks as well as studies in the literature may limit the differential diagnosis of dorsal column lesions to vitamin B12 deficiency, copper deficiency, and nitrous oxide toxicity.[9–12] Therefore, radiologists may be unaware that sensory neuronopathies should be included in the differential diagnosis of dorsal column lesions which can be longitudinally extensive.[9–14] As such, the diagnostic role of MRI may be overlooked.

Furthermore, there are unresolved and uncertain issues regarding the utility of spinal-cord MRI in the care of patients with sensory neuronopathies. First, no cases have described whether MRI can be used as a longitudinal marker to detect treatment efficacy. In such instances, the accompanying neurological examination and nerve-conduction studies should also improve, and would therefore support a potential role for MRI as a longitudinal marker. Furthermore, most studies have reported on spinal-cord MRI occurring at least 1 year to several years after the onset of a sensory neuronopathy.[1,15–20] Given such chronicity, it has been hypothesized that dorsal column lesions reflect a largely irreversible burden of gliotic injury. However, detecting imaging abnormalities in the earlier stages of a sensory neuronopathy would instead suggest an inflammatory burden of injury, which may be more treatment responsive.

In this report, we define how spinal-cord MRI can be used as a longitudinal marker of treatment efficacy in sensory neuronopathies, with imaging abnormalities detected in the earlier as well as chronic stages. Further diagnostic, mechanistic, and therapeutic implications are discussed. All patients provided informed consent to be included in this case series.

2. Case I

A 35-year-old, right-handed, Caucasian female was referred to our clinic for gait instability associated with labs showing anti-Ro/SS-A antibodies. She was in her usual state of health until 4 months prior to evaluation at our center, when over the course of 4 weeks, she developed acute onset of abdominal and back pain, diffuse truncal allodynia which resolved, and was replaced by dysesthesias affecting her right arm and both lower extremities (Fig. 1A, timeline of patient's history). Two months prior to evaluation, over the span of only 2 weeks, she developed impaired dexterity of her right hand, sensory ataxia affecting both legs, and rapid loss of the ability to independently ambulate. There was no urinary or fecal incontinence. She articulated a sensation of limb de-afferentation, and of not knowing where the lower extremities and the right upper extremity were in space. However, there was sparing of the left upper extremity.

Six weeks prior to evaluation at our clinic, she was diagnosed by an outside neurologist as having a sensory neuronopathy, based on characteristic clinical findings and nerve-conduction studies.[1–7,15] This included findings of diffuse arreflexia, asymmetric limb ataxia affecting the right > left upper extremities and both lower extremities, decreased joint position sense affecting the knees and right elbow, and a flail and functionally de-afferented right arm with pseudo-athetotic movements. Significantly, despite the onset of sensory neuronopathy symptoms occurring over only 2 months, she was virtually wheelchair-bound and was unable to ambulate more than 5 steps without 2-person assistance. In addition, nerve-conduction studies supported the diagnosis and reflected damage to large-sized DRG. There was inability to elicit any sensory nerve action potentials (SNAPs) in the lower extremities (sural nerves), and the right upper extremity (median, ulnar, and radial sensory nerves, Fig. 1B). There were preserved albeit decreased SNAPs in the clinically unaffected left upper extremity, and all compound motor action potentials were normal.

In these 6 weeks prior to evaluation at our center, her outside physicians had prescribed weekly courses of intravenous immunoglobulin (IVIg, weekly dose of 0.5 g/kg), which did not have any clinical benefit. One month prior to our evaluation, weekly intravenous pulses of 3000 mg methylprednisolone were added with no clinical improvement. Five courses of plasma exchange also did not provide any clinical benefit. She was therefore referred for further evaluation to our center.

Our clinical assessment was similar to the outside neurologist's evaluation. We noted a flaccid, de-afferented right upper extremity having pseudo-athetotic movements, arreflexia, lower-extremity sensory ataxia, and inability to even stand from a wheelchair without 2-person assistance.

Further serological studies noted the presence of anti-Ro/SS-A antibodies, antinuclear antibodies (ANA 1:40, speckled pattern), C4 hypocomplementemia, and polyclonal gammopathy. She otherwise did not have anti-La/SS-B antibodies, antibodies against other extractable nuclear antigens (i.e., anti-ENA antibodies), rheumatoid factor (RF), or cryoglobulins. A review of symptoms did not reveal evidence for a systemic rheumatic disease potentially associated with a sensory neuronopathy. In particular, there was no rash, photosensitivity, alopecia, joint pain, aphthous ulcers, serositis, Raynaud phenomenon, hematuria, or nephrolithiasis. The patient denied sicca symptoms, and had a normal Schirmer test with a nondiagnostic lip biopsy. However, the presence of an ocular staining score of 6, coupled with anti-Ro/SS-A antibodies, satisfied the 2016 ACR/EULAR (American College of Rheumatology and European League Against Rheumatism) classification criteria for primary SS.[21]

Serological workup and other ancillary studies excluded other causes of a sensory neuronopathy, with no evidence of an underlying infection (including human immunodeficiency virus),

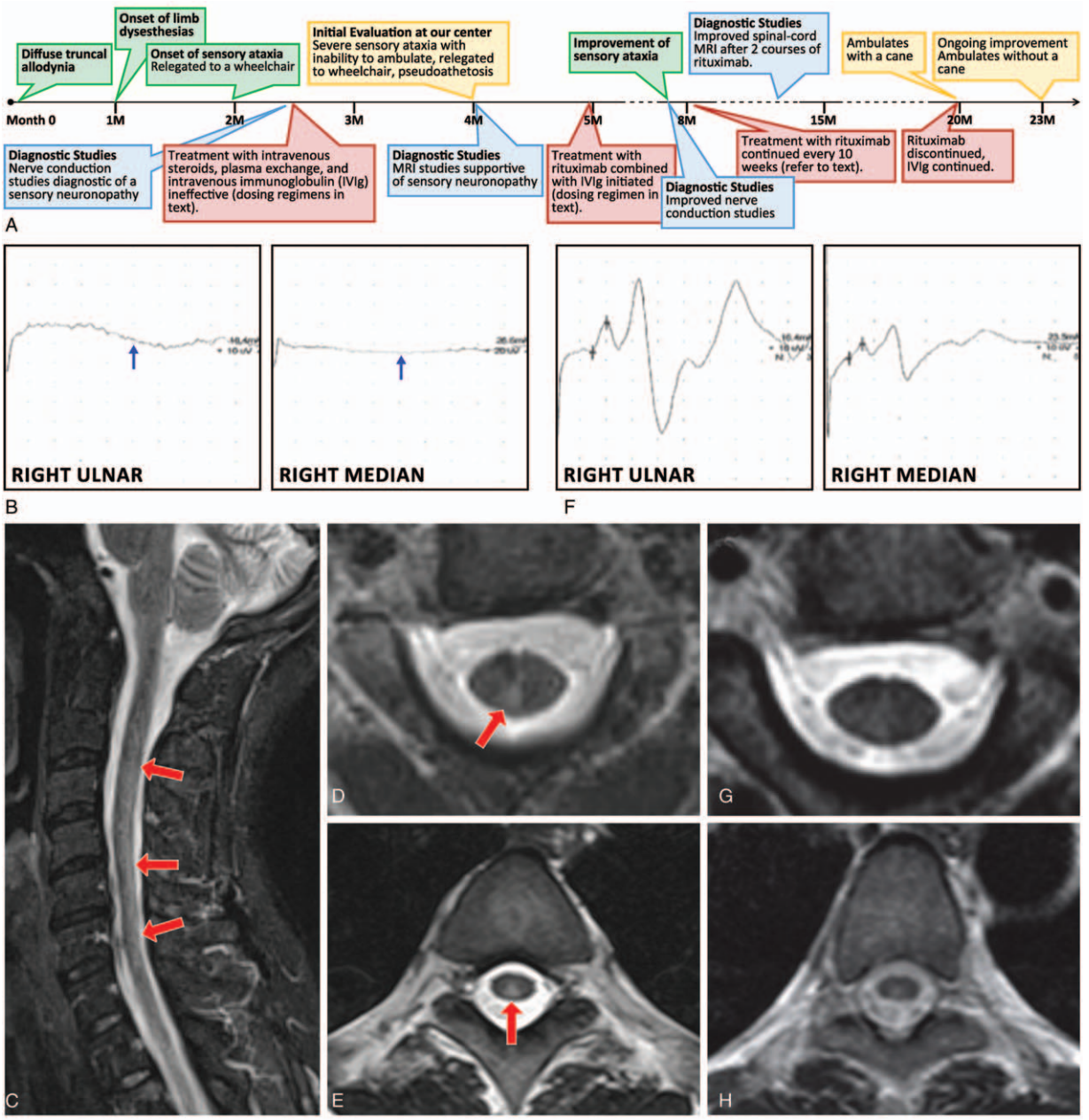

Figure 1. Timeline of disease, nerve-conduction, and neuroimaging studies in a sensory neuronopathy patient treated with rituximab combined with intravenous immunoglobulin. (A) Timeline of patient's symptoms, diagnostic studies, and response to treatment. (B) Prior to treatment, the sensory nerve action potentials (SNAPs) have a flat contour and are not elicited for the right ulnar sensory nerve (left panel) and right median sensory nerve (right panel). Such diffuse loss of SNAPs is characteristic of a sensory neuronopathy, and is also an electrodiagnostic indicator of large-sized, dorsal root ganglia neurodegeneration. Pretreatment MRI studies (C–E): Sagittal T2-weighted sequence shows hyperintense lesions, which are longitudinally extensive in the cervical and thoracic cord (red arrows) (C). Axial T2-weighted sequences show hyperintense lesions in the dorsal columns (red arrow), affecting the cuneate fasciculus as well as the gracile fasciculus in the cervical (D) and thoracic cord (E). In addition, on axial T2-weighted sequence of the cervical spinal-cord, there is asymmetric, hyperintensity affecting the right more than the left dorsal column (D). After 1 course of treatment, SNAPs can now be elicited from the right ulnar (left panel) and right median (right panel) sensory nerves (F), corresponding to patient's improvement on neurological examination and MRI studies. Post-treatment MRI studies (G and H): after 2 courses of treatment, axial T2-weighted sequences show interval decrease in dorsal column hyperintensities in the cervical (G), as well as thoracic cord (H). MRI = magnetic resonance imaging.

sarcoidosis (normal serum angiotensin converting enzyme and no hilar adenopathy on chest X-ray), celiac disease (no endomysial IgA/IgG antibodies), toxic exposure (i.e., vitamin B6 toxicity), or paraneoplastic syndromes (i.e., no antineuronal antibodies [ANNA-1, anti-Hu] assessed by a Mayo Clinic paraneoplastic panel and by normal computed tomography scan of the chest/abdomen/pelvis).

MRI of the spinal-cord was performed, and showed hyperintense lesions affecting the dorsal columns. These MRI findings are illustrated in Fig. 1C–E. Sagittal T2-weighted sequences show hyperintense lesions, which are longitudinally extensive (i.e., spanning more than 3 vertebral segments; Fig. 1C). Axial T2-weighted sequences show the dorsal column lesions affecting both the cuneate fasciculus (ascending sensory tracts from the

upper extremities), as well as the gracile fasciculus (ascending sensory tracts from the lower extremities), in both the cervical and thoracic cord (Fig. 1D and E). Intriguingly, these axial T2-weighted sequences show that there is asymmetric hyperintensity primarily affecting the right dorsal column in the cervical spinal-cord, but largely sparing the left dorsal column. This right-sided preponderance is strikingly congruous with this patient's presentation, given that she had severe limb ataxia primarily affecting the right upper extremity, and given that her nerve-conduction findings implicated more severe DRG injury in the right upper extremity. The thoracic spinal cord showed bilateral dorsal column lesions. There was no postgadolinium T1-weighted signal enhancement.

Significantly, the interpreting radiologist only listed vitamin B12 and copper deficiency as potential etiologies associated with these dorsal column lesions, but did not include sensory neuronopathies in the differential diagnosis. The patient had normal levels of vitamin B12 (including normal methylmalonic acid and homocysteine) and copper. Instead, our patient presented with anti-Ro/SS-A antibodies, a sensory neuronopathy, and SS. Therefore, with the diagnosis of SS and especially given the acuity and severity of her sensory neuronopathy, we elected to further treat her sensory neuronopathy as being immune mediated.

Cyclophosphamide was then considered but not used due to patient concerns regarding ovarian toxicity and fertility. Rituximab infusions were started within 1 month after evaluation at our center. The initial induction dose was 375 mg/m^2 per dose (585 mg) once a week for 2 weeks. The patient was continued on IVIg at a dose of 0.5 g/kg every 2 to 3 weeks (further details supporting this treatment regimen are included in Section 5). The patient was closely followed, and after 10 weeks of treatment, there was discernible improvement on her neurological examination. She was still arreflexic, had pseudo-athetotic movements of the right upper-extremity, was still largely confined to a wheelchair, but there was improvement in proprioception and sensory ataxia. Consequently, nerve-conduction studies were repeated. Previously undetected SNAPs were now able to be elicited. In addition to the right ulnar and median sensory nerve (Fig. 1F), SNAPs were now able to be elicited from the right radial sensory nerve.

Given such improved clinical and nerve-conduction findings, the patient was continued on rituximab at 375 mg/m^2 per dose (585 mg) every 10 weeks. A similar regimen has been used in other autoimmune neuromuscular disorders.[22] Axial T2-weighted MRI studies performed after 2 courses of rituximab (8 months of cumulative treatment, see timeline) showed interval decrease in dorsal column hyperintensity (Fig. 1G and H). After a total of 6 courses of rituximab therapy (15 months of cumulative therapy), she continued to have improvement, was able to ambulate with a cane, and pseudo-athetotic movements of the right upper extremity were no longer present. At this time, she articulated a wish to become pregnant. Therefore, there was a consensual decision to discontinue rituximab. The patient continues on IVIg at a similar dose, along with intensive physical therapy. When last evaluated 23 months after onset of symptoms, she continues to have persistent improvement in sensory ataxia. Notably, she is now able to ambulate without a cane on flat terrain.

3. Case II

A 69-year-old, right-handed, African-American female was referred for evaluation of gait instability associated with labs showing anti-Ro/SS-A antibodies.

The patient was in her usual state of health until 5 years prior to evaluation at our center, when over the course of 3 months, she developed dysesthesias in the hands and feet (Fig. 2A, timeline). Over the 2 years prior to evaluation, she suffered progressive gait impairment, falls, and loss of independent ambulatory capacity requiring constant use of a walker. There was no urinary or fecal incontinence. During this time, she also developed symptoms of dry eyes and dry mouth. In the year prior to our evaluation, her limb dysesthesias graduated from a sensation of numbness to burning pain.

Upon evaluation at our center, she had examination findings suggestive of a sensory neuronopathy. Similar to patient 1, she had preserved power, but marked loss of position sense which affected the knees and wrists, sensory ataxia, positive Romberg, and a wide-based gait requiring constant use of a walker. Diagnostic nerve-conduction studies are shown in Fig. 2B. Similar to patient 1, there was an absence of SNAPs in the lower extremities (sural nerves), and upper extremities (median, ulnar, and radial sensory nerves).

In addition, our patient developed a painful sensory neuropathy termed as a small-fiber neuropathy.[23,24] This neuropathy targets nociceptive, thinly myelinated A-delta, and unmyelinated C-fiber nerves. She experienced diffuse burning pain not conforming to a "stocking-and-glove pattern." As shown in Fig. 2C, punch skin-biopsy studies were diagnostic of a small-fiber neuropathy, and occurred in patterns suggestive of small-sized DRG injury (i.e., referred to as a nonlength-dependent small-fiber neuropathy).[25–31]

We established the diagnosis of SS based on a Schirmer evaluation revealing decreased tear production, the presence of anti-Ro/SS-A antibodies[21] and supportive findings including abnormal parotid scintigraphy.[32] Other serologic findings included ANA 1:40 (speckled pattern), negative RF, normal C3 and C4 complements, and polyclonal gammopathy. Apart from PNS disease (which interestingly antedated emergence of sicca symptoms), there was otherwise no end-organ findings indicative of systemic, extraglandular disease. Other disorders which may be associated with a sensory neuronopathy were excluded according to the evaluation detailed for patient 1.

An MRI of the spinal cord was performed, and the findings are shown in Fig. 2D and E. Sagittal T2-weighted sequences showed hyperintense lesions, which were longitudinally extensive (Fig. 2D). Axial T2-weighted sequences showed hyperintense lesions affecting both the cuneate fasciculus and the gracile fasciculus in the cervical cord (Fig. 2E). There was no postgadolinium T1-weighted signal enhancement. Similar to patient 1, the interpreting radiologist did not include a sensory neuronopathy in the differential diagnosis. Instead, the differential diagnosis was again limited to vitamin B12 deficiency and copper deficiency. The patient had normal serum levels of vitamin B12 and copper.

The patient reported neuropathic pain intensity as an 8/10 on the Visual Analogue Scale despite polysymptomatic therapy. Prior studies have suggested that SS patients who similarly present with nonlength-dependent, small-fiber neuropathies may have a significant analgesic response to IVIg, even when neuropathic pain has been refractory to polysymptomatic as well as other immunomodulatory strategies.[23,33–36] In addition, given this patient's multiple falls and constant ambulatory dependence on a walker, she had high-risk features portending eventual relegation to a wheelchair. Therefore, we started IVIg, given at 2 g/kg, on a monthly basis. She has been maintained on IVIg for 2 years. Although there has been no improvement in established neurological deficits, while on IVIg, she has not

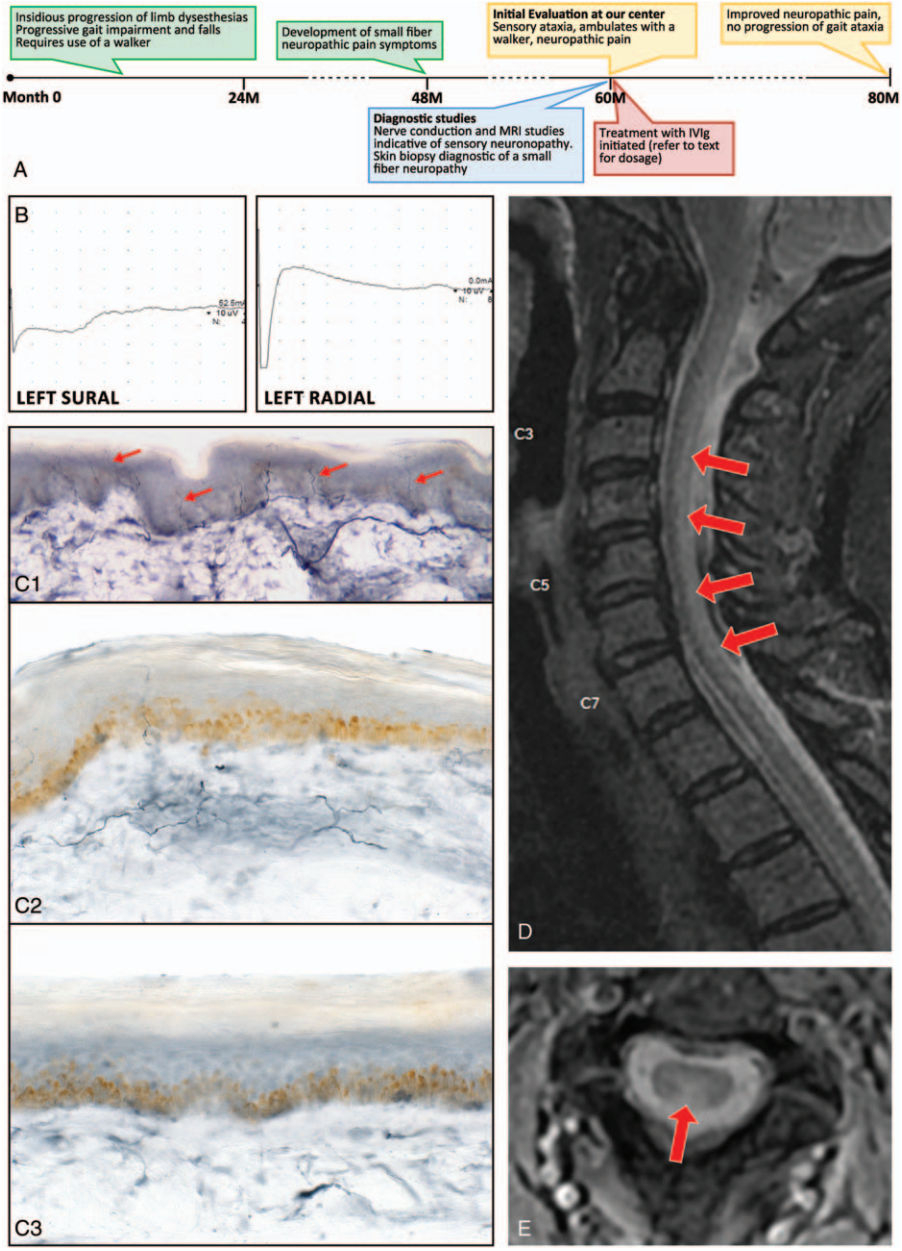

Figure 2. Timeline of disease, nerve-conduction studies, punch skin biopsy, and neuroimaging studies in a sensory neuronopathy patient treated with intravenous immunoglobulin (IVIg) therapy. (A) Timeline of patient's symptoms, diagnostic studies, and response to IVIg therapy. (B) The sensory nerve action potentials (SNAPs) have a flat contour and are not elicited for the left sural nerve (left panel) and left radial sensory nerve (right panel). Such diffuse loss of SNAPs is characteristic of a sensory neuronopathy, and is also an electrodiagnostic indicator of large-sized DRG neurodegeneration. (C) Punch skin-biopsy studies are diagnostic for a small-fiber neuropathy when there is decreased intraepidermal nerve-fiber density (IENFD) of unmyelinated nerves. Unmyelinated C-fiber nerves are immunostained against the panaxonal protein PGP 9.5. In a skin biopsy taken from a patient without a small-fiber neuropathy, there is normal, IENFD of unmyelinated nerves (thin red arrows) (C1). By contrast, (C2) and (C3) are reflective of skin-biopsy specimens from our patient, which are diagnostic of a nonlength-dependent, small-fiber neuropathy. Compared with the normal control, there is markedly decreased IENFD in biopsies taken from the proximal thigh (C2), as well as the distal leg (C3). This pattern of disproportionately reduced IENFD in both the proximal thigh and distal leg is a surrogate marker of small-sized DRG neurodegeneration. Magnetic resonance imaging studies (D and E): sagittal T2-weighted sequences show hyperintense lesions, which are longitudinally extensive (thick red arrows) (D). Axial T2-weighted sequences show hyperintense lesions affecting both the cuneate fasciculus and gracile fasciculus of the cervical cord (thick red arrow) (E). DRG = dorsal root ganglia.

experienced further gait deterioration or new neurological deficits. Similarly, her neuropathic pain has substantially improved. The pain intensity is now only a 3/10 on the Visual Analogue Scale. The preferential use of IVIg in SS patients with sensory neuronopathies and nonlength-dependent, small-fiber neuropathies is further considered in Section 5.

4. Case III

A 55-year-old, right-handed, Caucasian female was referred for evaluation of gait instability associated with anti-La/SS-B antibodies. The patient was in her usual state of health until 3 years prior to our evaluation, when she developed dysesthesias concomitantly and symmetrically affecting the hands, thighs, and

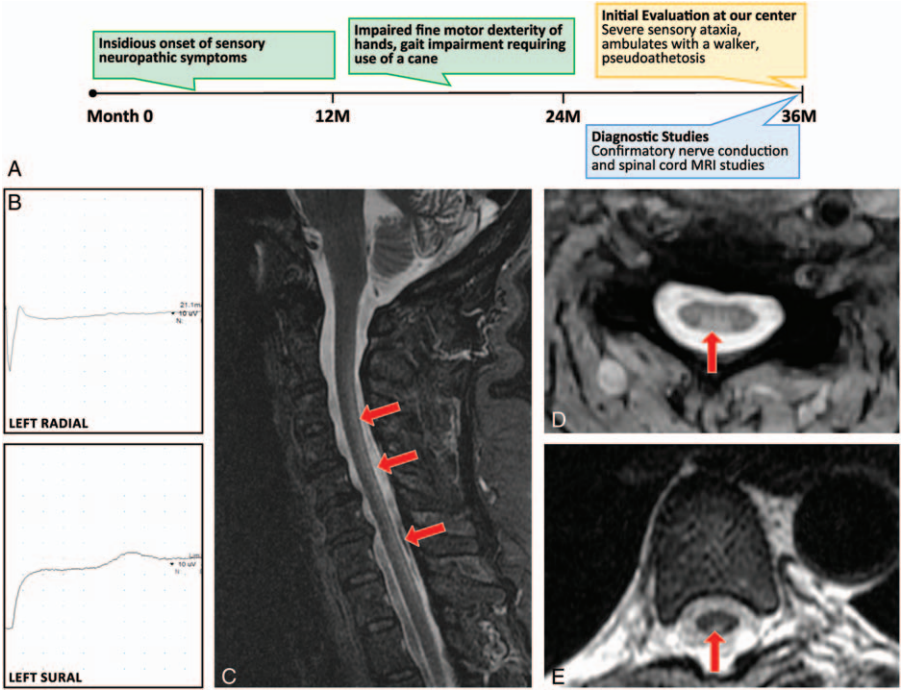

Figure 3. Timeline of disease, nerve-conduction, and neuroimaging studies in a sensory neuronopathy patient. (A) Timeline of patient's symptoms and diagnostic studies. (B) The sensory nerve action potentials (SNAPs) have a flat contour and are not elicited for the left radial sensory nerve (top panel) and left sural nerve (bottom panel). Such diffuse loss of SNAPs is characteristic of a sensory neuronopathy, and is also an electrodiagnostic indicator of large-sized dorsal root ganglia neurodegeneration. Magnetic resonance imaging studies (C–E): sagittal T2-weighted sequences show hyperintense lesions which are longitudinally extensive (red arrows) (C). Axial T2-weighted sequences show hyperintense lesions affecting both the cuneate fasciculus and gracile fasciculus of the cervical (D) and thoracic cord (E) (red arrows).

feet (Fig. 3A, timeline). Over the ensuing 2 years prior to our evaluation, she gradually developed impaired dexterity of hands, had difficulty buttoning and holding utensils, and experienced gait impairment. She described a sensation of not knowing the position of her feet in space, and required the use of a cane. There was no weakness, and no urinary or fecal incontinence.

Upon evaluation at our center, her neurological evaluation revealed findings which were consistent with a sensory neuronopathy. She had preserved power, diffuse arreflexia, loss of position sense affecting the knees and elbows, and pseudoathetotic movements in the upper extremities. Her gait examination demonstrated a positive Romberg, a wide-based unsteady gait, constant use of a cane, and the inability to tandem walk. Her nerve-conduction studies were consistent with a sensory neuronopathy as described for the previous patients (Fig. 3B). There was absence of SNAPs affecting sensory nerves in the lower extremities (sural nerves), and upper extremities (median, ulnar, and radial sensory nerves).

Although she had anti-La/SS-B antibodies, the diagnosis of SS was excluded based on the absence of sicca symptoms, an ocular staining score of 0, and a nondiagnostic lip biopsy. She otherwise did not have anti-Ro/SS-A antibodies, antinuclear antibodies, RF, polyclonal gammopathy, low complements, or cryoglobulins. A review of symptoms did not reveal evidence for a systemic rheumatic disease potentially associated with a sensory neuronopathy. In particular, there was no alopecia, joint pain, rash, photosensitivity, aphthous ulcers, serositis, Raynaud phenomenon, hematuria, or nephrolithiasis. Her workup excluded other causes of a sensory neuronopathy as described for patient 1.

We next performed MRI of the spinal cord, and the results of these studies are shown in Fig. 3C–E. Similar to patients 1 and 2, sagittal T2-weighted sequences showed hyperintense lesions, which were longitudinally extensive (Fig. 3C). Axial T2-weighted sequences showed hyperintense lesions affecting both the cuneate fasciculus and the gracile fasciculus in the cervical and thoracic cord (Fig. 3D and E). There was no postgadolinium T1-weighted signal enhancement. Similar to patients 1 and 2, the diagnosis of a sensory neuronopathy was not included in the radiologist's differential diagnosis, which was again limited to copper and vitamin B12 metabolic deficiencies. Vitamin B12 and copper levels were normal in this patient. We are now actively trying to obtain insurance approval for IVIg therapy. The rationale for IVIg therapy is detailed in Section 5.

5. Discussion

We here describe how spinal-cord MRI can facilitate diagnosis and management in a case series of 3 patients with sensory neuronopathies. There were several important findings. First, we define shared imaging findings between all 3 patients, which can be integrated with nerve-conduction studies to expedite diagnosis. Second, we provide the first demonstration that spinal-cord MRI can be used to help substantiate treatment response. Finally, we describe how the association of sensory neuronopathies with antibodies and skin biopsy may have diagnostic utility and provide additional insight into mechanisms of DRG degeneration. Further implications of our findings are discussed below.

All 3 patients presented with characteristic findings of a sensory neuronopathy, including sensory ataxia, profound kinesthetic impairment, and arreflexia. Nerve-conduction studies revealed diffuse absence of SNAPs illustrative of large-sized DRG degeneration. In these patients, characteristic MRI findings included dorsal column lesions, with involvement of both gracile fasciculus (lower extremity) as well as cuneate fasciculus (upper extremity) tracts. These lesions were longitudinally extensive, and reflect how degeneration of central afferent tracts between DRG and dorsal columns can be a systemic process. Interestingly, patient 1 preferentially had dorsal column lesions affecting the right side of the cervical spinal-cord, which was associated with more severe clinical and nerve-conduction findings in the right upper-extremity. The thoracic spinal cord showed bilateral involvement of the cuneate and gracilis fasciculi. In all of our patients, the diagnosis of a sensory neuronopathy was not included in the differential diagnosis of dorsal column lesions, with radiologists only mentioning the possibility of vitamin B12 and copper deficiency. This omission is recapitulated in the literature, in which review articles as well as radiology textbooks may not include sensory neuronopathies in the differential diagnosis of dorsal column or longitudinally extensive lesions.[9–14] However, other studies have suggested a promising diagnostic role for spinal-cord MRI neuroimaging. Whereas Camdessanche reported that 5% of sensory neuronopathy patients had abnormal spinal-cord MRI studies,[37] most other studies reporting on more than 10 patients have reported that 50% to 85% of sensory neuronopathy patients have abnormal spinal-cord MRI studies.[15–18,38–40] Therefore, our findings reaffirm how the multidisciplinary group of physicians who may encounter sensory neuronopathies can recognize and utilize spinal-cord MRI as a valuable adjunctive marker. Furthermore, our study describes how spinal-cord MRI can be used as a longitudinal indicator of treatment efficacy. In patient 1, in response to immunomodulatory therapy, improvement in dorsal column lesions was associated with decreased sensory ataxia and improved ambulation. In the only study which assessed serial MRI studies in response to immunomodulatory therapy, unsuccessful treatment with prednisone monotherapy was associated with more extensive dorsal column lesions on post-treatment spinal-cord MRI.[20] Therefore, our study now suggests how serial MRI neuroimaging can be integrated with nerve-conduction findings to help evaluate treatment efficacy.

Our findings illustrate how MRI neuroimaging can be integrated with other studies to further identify mechanisms and therapeutic approaches. Patients 2 and 3 are representative of most reported cases in the literature, in which MRI was performed 1 year to several years after onset of sensory neuronopathy symptoms.[1,15–20,41] In such cases, postmortem studies have correlated MRI dorsal column lesions with irreversible gliosis of dorsal horns.[42] In this scenario, immunomodulatory therapy may not be expected to reverse debility, but may prevent further deterioration (i.e., IVIg in patient 2). By contrast, patient 1 reflects the most rapid interval in the literature reported between onset of sensory neuronopathy symptoms and performance of MRI. In this acute setting, the response to immunomodulatory therapy suggests that dorsal column lesions in this earlier stage may reflect treatment-responsive inflammation.

Patient 1 had a significant response after the first course of rituximab (375 mg/m^2 per dose [585 mg] once a week for 2 weeks), with notable improvement on neurological examination and the ability to elicit previously unobtainable SNAPs. There was ongoing improvement during the course of additional rituximab and ongoing IVIg therapy. We acknowledge the possibility that such improvement was solely due to rituximab, and not combination therapy with IVIg. However, we thought that there were several reasons why it was important to continue cotreatment with IVIg. Prior reports describing rituximab in sensory neuronopathy were not entirely representative of patient 1, instead including neuronopathy patients with milder[43] or more indolent disease,[44] and despite treatment could have persistent or worsening clinical deficits.[43,45] By contrast, cotreatment of IVIg with rituximab can induce therapeutic synergy.[46,47] In other autoimmune disorders, rituximab is used as step-up therapy, added to and not necessarily replacing prior immunomodulatory therapy.[48] Rituximab was discontinued after 6 courses, given the patient's pregnancy wishes as well as her significant clinical improvement. We have since continued with IVIg therapy, and at the time of last evaluation she was ambulating without a cane. Careful longitudinal assessment will evaluate whether her reconstituted B-cells are more tolerant and will permit the ongoing use of IVIg therapy.

Our study also illustrates an important role for defining the potential relationship of autoimmunity with sensory neuronopathies. Whereas autoantibodies may reflect a definable autoimmune disease (patients 1 and 2), sensory neuronopathy patients may also have antibodies in the absence of an autoimmune disease (patient 3). In the case of patient 1, it is important to use the 2016 ACR/EULAR classification criteria to define that the patient's sensory neuronopathy was due to SS.[21] Although patient 1 did not experience any sicca symptoms, the 2016 ACR/EULAR classification criteria no longer include symptoms of dry eyes and dry mouth. Instead, these criteria allow the diagnosis of SS to be ascertained based on 2 features seen in patient 1, which included an ocular staining score of $\geq$5 and findings of anti-Ro/SS-A antibodies. The utility of these updated criteria are substantiated in our patient's case, given that her sensory neuronopathy had a robust response to B-cell depleting therapy. Therefore, sensory neuronopathies occurring in the context of anti-Ro/SS-A antibodies should prompt further evaluation for primary SS, according to the 2016 ACR/EULAR classification criteria.[21] In other situations, the occurrence of anti-Ro/SS-A antibodies without SS may still support that a sensory neuronopathy is immune-mediated and may antedate eventual emergence of SS, even by up to a decade.[5,23,38,49–51]

The assessment for RF in SS is particularly important, given that its frequency has been reported in between 40% and 60% of patients, and given its association with extraglandular complications and with cryoglobulins (particularly in the context of low C4 levels).[52] In addition, other studies have shown that RF may be a prognostic marker for a higher risk of lymphoma.[53] In our study, no patients had RF. However, despite not being part of the 2016 ACR/EULAR classification criteria for primary SS,[21] further studies evaluating the association of SS with MRI markers of a sensory neuronopathy should also focus on the potential presence of RF.

Patient 3 reflects the importance for defining the relationship between anti-La/SS-B antibodies, sensory neuronopathy, and SS, even if such anti-La/SS-B antibodies are no longer part of the 2016 ACR/EULAR classification criteria for primary SS.[21] Patient 3 had isolated presence of anti-La/SS-B antibodies and did not satisfy SS classification criteria. Based on one perspective, the presence of anti-La/SS-B antibodies may suggest that the sensory neuronopathy is immune-mediated or may antedate emergence toward SS diagnosis. However, another perspective is based on

SS disease activity (EULAR Sjögren Syndrome Disease Activity Index)[54] in which sensory neuronopathy is weighted as reflecting high PNS disease activity. In such cases, there may be heightened diagnostic suspicion for SS based on the accompanying presence of antibodies or B-cell activation markers such as high-titer ANA, RF, cryoglobulins, or low complement levels. As noted for patient 3, she did not have evidence for these immunological markers. However, further evaluation should then focus on whether patients with anti-La/SS-B antibodies, sensory neuronopathies, and presumed as being negative for anti-Ro/SS-A antibodies may in fact have anti-Ro52 and/or anti-Ro60 antibodies.[55] In our case, the commercial laboratory did not further assess for anti-Ro52 or anti-Ro60 antibodies. Therefore, subsequent studies should try to assess for anti-Ro52 and anti-Ro60 antibodies in SS neuronopathy patients who are seronegative for anti-Ro/SS-A antibodies but have isolated anti-La/SS-B antibodies.

Finally, as also illustrated in patient 2, skin-biopsy should be considered in patients with sensory neuronopathies and potential small-fiber neuropathies. Such skin-biopsy studies can identify patterns of small-sized DRG degeneration,[25–31] may complement MRI findings in which dorsal column lesions stem from large-sized DRG injury, but has not been used in MRI case series of sensory neuronopathy patients.

Given that our study is a case series, larger studies are needed to define the role of spinal-cord MRI in the diagnosis and follow-up of sensory neuronopathy patients, and of IVIg and rituximab as cotreatment in the management of immune-mediated sensory neuronopathies. We also acknowledge that the natural course of spinal-cord neuroimaging findings in untreated sensory neuronopathy patients is not known. However, we consider it unlikely that the improvement of MRI studies in patient 1 is unrelated to treatment, given that there was also an associated improvement in nerve-conduction studies.

In summary, we have demonstrated in this case series of 3 sensory neuronopathy patients how spinal-cord MRI can facilitate diagnosis, but may not be considered in the differential diagnosis of dorsal column lesions. Prompt recognition that dorsal column lesions may reflect a sensory neuronopathy is particularly important, given that earlier stages of disease may respond to immunomodulatory therapy. In conjunction with nerve-conduction studies, spinal-cord MRI can now be investigated as a longitudinal indicator of treatment efficacy.

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