CISP-Plus: Expanding the Spectrum of Chronic Immune Sensory Polyradiculopathy (CISP)

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Abbreviations: CISP = chronic immune sensory polyradiculopathy, CIDP = chronic inflammatory demyelinating polyradiculoneuropathy, CISMP = chronic immune sensorimotor polyradiculopathy, EFNS = European Federation of Neurological Societies, EMG = needle electromyography, IVIG = intravenous immunoglobulin, IVMP = intravenous methylprednisolone, MF = myelinated fibers, NCS = nerve conduction studies, NS = non-statistically significant, PNS = Peripheral Nerve Society, QST = quantitative sensory testing, SSEP = somatosensory evoked potential.

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Abstract

Objectives: Sensory loss with normal nerve conduction studies (NCS) from focal sensory root inflammatory demyelination is characteristic of chronic immune sensory polyradiculopathy (CISP). However, non-pure cases involving motor and distal sensory nerves exist (CISP-plus). We hypothesize that CISP-plus and CISP are fundamentally part of the same syndrome through comparison of clinical, neurophysiological and pathological features.

Methods: CISP-plus (primary dorsal root with lesser motor and sensory nerve involvement) and CISP cases were retrospectively analyzed (1986-2019).

Results: We identified 44 CISP-plus and 28 CISP cases (n=72) with 86% (38/44) of CISP-plus and 79% (22/28) of CISP patients experiencing imbalance. On examination, large fiber sensory loss was present in 98% (43/44) of CISP-plus and 96% (27/28) of CISP. Gait ataxia was evident in 93% (41/44) of CISP-plus and 79% (22/28) of CISP. Mild distal weakness was common in CISP-plus (75%, 33/44). NCS showed mild abnormalities in all CISP-plus and were normal (by definition) in all CISP. Elevated cerebral spinal fluid (CSF) protein, slowing of somatosensory evoked potentials and MRI root enhancement occurred in most CISP-plus and CISP cases. Eleven CISP-plus nerve biopsies showed loss of large myelinated fibers and onion-bulb formation most prominent in rootlet biopsies. Immunotherapy resulted in marked improvement of gait ataxia in 84% (27/32) of CISP-plus and 93% (14/15) of CISP cases with return to normal neurological examination in half (25/46).

Conclusion: The recognition of CISP-plus expands the spectrum of CIDP by combining CISP-plus (predominant sensory polyradiculopathy with mild motor and sensory nerve involvement) with pure-CISP (focal sensory polyradiculopathy) together as proximal sensory CIDP.

Introduction
Although chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) usually presents with weakness\(^1,2\), sensory-predominant forms have been described\(^3,4\) including the recently recognized paranodal neuropathies (contactin-1 associated CIDP)\(^5,6\). In 2004, our group described a restricted form of sensory CIDP, chronic immune sensory polyradiculopathy (CISP), characterized by selective involvement of sensory nerve roots.\(^7\) A similar acute form of immune-mediated pure-sensory polyradiculopathy has recently been described (Vazquez do Campo et al, Muscle and Nerve, in press). CISP presents with sensory loss, gait ataxia, falls, large fiber sensory deficits, reduced reflexes and preserved muscle strength. Because the pathology is confined to sensory roots (preganglionic) and motor nerves are spared, nerve conduction studies and electromyography (NCS/EMG) are normal.\(^7\) The presence of slowed somatosensory evoked potentials (SSEP), elevated cerebral spinal fluid (CSF) protein and enlarged dorsal roots on MRI support the diagnosis of CISP.\(^8\)\(^\text{-}11\) Dorsal lumbar rootlets biopsies confirm inflammatory demyelination.\(^7\) CISP has been recognized as atypical CIDP and is included in the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) CIDP criteria.\(^12\) Since CISP’s description, we have noted patients with a similar clinical syndrome but with mild distal weakness and mild abnormalities on NCS implying the pathology is not restricted to sensory nerve roots (Figure 1A, right panel). We call this non-pure form, CISP-plus.

The purpose of our current study is to introduce and define the entity of CISP-plus by presenting a cohort of CISP-plus cases and comparing their clinical, neurophysiological, pathological and radiological characteristics and treatment response to a cohort of CISP cases.

Materials and Methods

Standard Protocol Approvals, Registrations, and Patient Consents.

The Mayo Clinic Institutional Review Board approved human specimen acquisition and review of patients’ histories. We retrospectively reviewed Mayo Clinic, Rochester database for coded diagnosis of CIDP, polyganglionopathy, sensory neuropathy, sensory ataxia and CISP from 1986 to 2019. Medical records of 16,542 potential patients were identified and reviewed; only patients who fulfilled our inclusion criteria and were evaluated by a neurologist were included. We reviewed NCS/EMG,
SSEP, quantitative sensory testing (QST), autonomic reflex screen, nerve biopsies, MRIs, CSF testing and serology for paraneoplastic or autoimmune causes of sensory neuropathy.

Clinical Criteria

CISP patients were defined using the previously published criteria: 1) a sensory syndrome without weakness; 2) normal NCS/EMG studies; 3) imaging studies (usually MRI) that exclude brain, cerebellum, spinal cord, or compressive nerve root lesions that could explain the clinical syndrome, and 4) SSEP or imaging abnormalities (usually MRI) consistent with nerve root involvement. CISP-plus patients were defined using the following criteria: 1) a predominant sensory syndrome with only mild distal or no weakness; 2) mild abnormalities on NCS/EMG (motor and/or sensory) that do not fully explain the clinical syndrome (including reduced compound muscle action potentials and sensory nerve action potentials [taking normal age values into account]); 3) imaging studies (usually MRI) that exclude brain, cerebellum, spinal cord, or compressive nerve root lesions that could explain the clinical syndrome, and 4) SSEP or imaging abnormalities (usually MRI) consistent with nerve root involvement. Sensory gait ataxia was defined as impaired Romberg test, abnormal tandem walking or marked difficulty walking without assistance with normal muscle strength and cerebellar function.

Patients in whom the pathological process was predominantly localized to the peripheral nerves were excluded. Excluded diagnoses included typical sensory CIDP, sensory neuronopathy (Sjogren's and paraneoplastic syndromes), or known causes of neuropathy including uremia, alcoholism, vitamin deficiency, heavy metal intoxication, collagen vascular diseases, thyroid disease, and hereditary neuropathies. Cases with diabetes mellitus were excluded unless the neurological syndrome predated the diabetes.

Physiological testing and Imaging

NCS/EMG and SSEP studies were performed using Mayo Clinic laboratory normal values and Nicolet Viking EDX (Natus Neurology, Madison, WI) and Cadwell Sierra Summit (Cadwell Industries, Inc., Kennewick, WA). QST was performed on the dorsal foot with CASE IV system (WR medical electronics, Maplewood, MN).
Autonomic testing was performed using autonomic reflex screen (WR medical electronics, Maplewood, MN).  

MRIs from CISP-plus and CISP patients including spine, plexus and peripheral nerves were reviewed blinded to the final diagnosis by two authors (SS and KA). All studies were screened for increased T2 signal, contrast enhancement within nerves or roots and clumping or thickening of roots.

Nerve Histology

Nerve biopsies were performed and processed in our peripheral nerve laboratory using standard histologic and immunohistochemistry stains (CD45, CD68) prepared on paraffin sections. Semithin epoxy sections were stained with methylene blue. Teased fibers were prepared and graded by previously defined pathologic criteria. Morphometric analysis was performed on epoxy sections using our Imaging System for Nerve Morphometry.

Provided the identity of the public trials registry and the clinical trial identifier number (if applicable).

Obtained authorization for disclosure (consent-to-disclose) of any recognizable persons in photographs, videos, or other information that may be published in the Journal, in derivative works by the AAN, or on the Journal's Web site (when applicable).

Data Availability

De-identified data are available upon a reasonable request.

Results

Summary of demographic data

We identified 44 CISP-plus and 28 CISP (total=72) cases. 15/28 of CISP cases have previously been reported. The median time from first neurological documented visit to final follow-up was 19 months (range: 1-287) for all cases; 25 months for CISP-plus and 18 months for CISP (p=0.002). The median age of onset overall was 58 years.
(range: 18-80); 60 years (range: 40-81) for CISP-plus and 57 years (range: 18-80) for CISP. There were 44 males (61%) overall with 28 males (64%) in CISP-plus cohort and 16 males (57%) in CISP cohort. The median duration of symptoms overall was 36 months (range: 1-360); 48 months (range: 1-360) in CISP-plus and 24 months (range: 1-216) in CISP. The overall median time from symptom onset to diagnosis for the combined groups was 3 years (range: 1-30); 4 years for CISP-plus (range 1-30) and 2 years for CISP (range: 1-18) (p=0.06) with 12 patients having very delayed diagnosis of more than 10 years after symptom onset (4 CISP and 8 CISP-plus); Figure 2.

**Clinical manifestations with sensory predominant presentations**

All CISP-plus and CISP cases (n=72) had progressive sensory predominant presentations. Patients presented with symptoms of gait imbalance (often debilitating) and sensory loss in 85% (61/72) overall; 86% (38/44) in CISP-plus and 79% (22/28) in CISP cases. Falls were common and reported in 57% (41/72) of cases overall; 57% (25/44) in CISP-plus and 57% (16/28) in CISP cases. Use of gait aids was necessary for almost half of cases; 45% (29/64) patients overall required gait aids: 46% (19/41) of CISP-plus and 43% (10/23) of CISP cases. More specifically, 27% (11/41) of CISP-plus and 26% (6/23) of CISP used canes (p= NS), 10% (4/41) of CISP-plus and none (0/23) CISP used walkers, and 12% (5/41) of CISP-plus and 18% (4 /22) of CISP used wheelchairs (p= NS). Prickling paresthesia was commonly reported in 77% (34/44) of CISP-plus and in 68% (19/28) of CISP cases (p= NS). In contrast, troublesome neuropathic pain at presentation was uncommon, reported by only 5% (2/44) CISP-plus and no CISP patients (p= NS). Overall, symptoms of CISP-plus were very similar to CISP.

Proprioception or vibration loss (large fiber modalities) were the most common findings on neurological examination present in 97% (70/72) cases overall; 98% (43/44) in CISP-plus and 96% (27/28) in CISP cases (p= NS). Reduced or absent deep tendon reflexes (knees or ankle) were evident in 90% (65/72) of cases overall; 89% (39/44) in CISP-plus and 93% (26/28) in CISP cases. Sensory gait ataxia was noted on examination in 88% (63/72) overall; 93% (41/44) in CISP-plus and in 79% (22/28) in CISP cases. In CISP-plus 66% (25/38) had positive Romberg testing and 70% (19/27)
had a pathological tandem walk, whereas in CISP 65% (13/20) had positive Romberg testing (n= NS) and 60% (12/20) had a pathological tandem walk (p= NS). By definition, no cases of CISP had weakness on neurological examination (0/28), however 75% (33/44) of CISP-plus cases had mild weakness involving distal lower limb segments (limited to mild weakness of toe flexors or extensors); p<0.001). Neurological examination findings were similar except for mild distal weakness in CISP-plus.

**Neurophysiological evaluation: NCS/EMG, SSEP, QST, and autonomic testing**

All 72 cases had NCS/EMG performed at our EMG lab within a year of the time of diagnosis. By definition, all CISP cases (28/28) had normal NCS/EMG in terms of the sensory syndrome (two had separate, co-existing chronic L5 radiculopathy on EMG findings). Minimal NCS abnormalities were present in all CISP-plus cases (44/44), characterized by: mildly prolonged F-wave latencies in 73% (32/44); reduced motor and sensory amplitudes in 57% (25/44) and 57% (25/44), respectively; mild slowing of motor conduction velocities in 41% (18/44) and mild slowing of sensory conduction velocities in 68% (30/44). None of the CISP-plus patients met the EFNS/PNS electrophysiological criteria for CIDP\textsuperscript{12} and in no cases were the electrophysiological abnormalities significant enough to explain the severe clinical sensory symptoms and signs (especially sensory ataxia). All 72 patients had preserved or normal for age sural sensory nerve action potentials (5 CISP-plus and 0 CISP patients older than 60 years had absent sural potentials which is normal for age in our laboratory). Needle EMG was normal in the majority (38/44) of CISP-plus patients with 6/44 cases demonstrating a mild motor polyradiculopathy with sparse fibrillation potentials confined to distal muscles (in feet more than hands) on needle examination that was interpreted as having minimal clinical relevance.

SSEP were performed in 40 CISP-plus and in 23 pure CISP patients. Overall, 76% (48/63) of patients showed SSEP abnormality; 78% (31/40) of CISP-plus and 74% (17/23) of CISP patients had slowing of SSEP (p= NS). In median CISP-plus studies, 56% (18/32) were abnormal and in tibial studies, 91% (30/33) were abnormal. In comparison, 50% (8/16) and 94% (15/16) of median and tibial CISP studies, respectively, were abnormal (p= NS). More specifically, in abnormal median studies,
61% (11/18) of CISP-plus and 88% (7/8) of CISP had prolonged N13 (cervical) latencies or prolonged N9-N13 interpeak latencies (segments that include cervical roots); Figure 1B. In addition, 33% (6/18) of CISP-plus and 13% (1/8) CISP had non-localizable median slowing. One CISP-plus median study showed mild prolongation of the N9 latency (clavicular response) in keeping with slowing of peripheral nerves. In the tibial studies, 27% (8/30) CISP-plus and no (0/15) CISP had prolonged N22 (lumbar spine) potentials (segment containing lumbar roots) and 73% (22/30) of CISP-plus and 100% (15/15) of CISP had poorly localizable slowing.

QST was performed in 33/44 of CISP-plus and in 14/28 of CISP patients. In CISP-plus patients, 88% (29/33) had abnormalities with large fiber modalities (reduced vibration in 64% [n=21/33] and light touch in 54% [n=18/33]) being somewhat more affected than small myelinated (reduced cooling in 48% [n=16/33]) or unmyelinated fiber modalities (reduced heat pain in 24% [hypoalgesia, n=8/33] and increased heat pain in 9% [hyperalgesia, n=3/33]). Similarly, in CISP patients, 93% (13/14) had abnormalities with large fiber modalities (reduced vibration in 86% [n=12/14] and touch in 50% [n=7/14]) being more affected than small myelinated (reduced cooling in 36% [n=5/14]) or unmyelinated fiber modalities (reduced heat pain in 7% [hypoalgesia, n=1/14] or increased heat pain in 14% [hyperalgesia, n=2/14]). These results indicate in both groups large myelinated sensory fibers are more involved than small myelinated or unmyelinated sensory fibers.

Autonomic reflex screen was performed in 29 CISP-plus and 10 pure-CISP patients. The median composite autonomic scoring scale (CASS) score for CISP-plus was 2 (range: 0-7) and for CISP was 0 (range:0-4). This indicates mild autonomic involvement for both groups, similar to the minimal autonomic involvement seen in CIDP.

Nerve Pathological Findings

Nerve biopsies from 11 CISP-plus patients were re-graded by two authors (KS and PJBD). No additional CISP nerve biopsies than previously reported were performed. The biopsied CISP-plus nerves included 3 lumbar dorsal rootlet, 2
fascicular sciatic, and 6 distal cutaneous nerve biopsies (1 superficial radial and 5 sural). Electron microscopy was performed in 3 rootlets, 1 sciatic, 1 superficial radial and 1 sural nerve. Teased fiber preparations were performed in all and showed increased rates of segmental demyelination highest in rootlet biopsies (mean 21%; range: 9-33%), next highest in sciatic biopsies (mean 15%; range: 14-16%), and lowest in distal cutaneous biopsies (mean 3%; range: 0-12%, Figure 3). Onion-bulbs were seen on teased preparations from rootlet biopsies (Figure 3A-B).

Morphometric analysis was performed on all 11 CISP-plus biopsies and the overall density of myelinated fibers (MF) was normal or mildly reduced (Figures 4 and 5). The main pathological finding was reduced density of large myelinated nerve fibers, more pronounced in proximal biopsies and less evident in distal biopsies, confirmed by fiber size histograms. Hence, all rootlet biopsies had unimodal small fiber peaks (Figure 4B-D). Of 2 sciatic biopsies, one had a unimodal small fiber peak (Figure 5B), whereas the other had an abnormal bimodal distribution with the large fiber peak occurring at a smaller fiber size than normal. In the 6 distal cutaneous nerve biopsies, 2 biopsies (1 superficial radial and 1 sural) had unimodal small fiber peaks (Figure 5C-D), another had the large fiber peak occurring at smaller fiber size than normal and the other 3 had normal fiber size distributions.

Onion-bulb formations were found frequently in proximal biopsies. Two of the 3 lumbar rootlet biopsies had dense large onion-bulb formations (Figure 4C-D, Figure 6A-B), one sciatic biopsy had frequent moderate-sized onion-bulb formations (Figure 5D and Figure 6C-D), while no distal cutaneous biopsies had frequent onion-bulbs formations (although rare small onion-bulbs were seen) (Figure 6G-H). Some fibers had myelin that was too thin for the axonal size, especially in proximal biopsies, suggesting remyelination. Abnormal degrees of scattered endoneurial inflammation were seen in all but one sural biopsy (Figure 3F-G). The CISP-plus biopsies were compared to 3 previously published lumbar rootlet CISP biopsies and 3 post-mortem lumbar rootlet controls. The rootlet biopsies from CISP-plus and CISP were very similar with loss of large fibers, unimodal small myelinated fiber size distribution and onion-bulb formations, whereas the controls all had normal bimodal distribution (small and large myelinated fiber peaks) and no onion-bulb formations (Figure 4A).
CSF and MRI radiology evaluations

CSF studies were performed in all 44 CISP-plus and in 26 CISP patients. The median CSF protein was 67 g/dl (range: 19-455) in CISP-plus and 71.5 g/dl (range: 31-161) in CISP (p= NS). Overall, 95% (42/44) of CISP-plus and 92% (24/26) of CISP had elevated CSF proteins. Six patients (5 CISP-plus and one CISP) had a mild lymphocytic pleocytosis (median 12 cells/ mm3; range: 4-44).

In CISP-plus, lumbar spine MRI was available in 36 patients, 33 with contrast. The most common abnormality was nerve root enhancement (axial images) in 73% (24/33) followed by thickening or clumping of nerve roots in 55% (20/36) and cauda equina enhancement (sagittal images) in 24% (8/33). Among CISP patients, 21 had imaging available, 14 with contrast. The most common abnormality was thickening or clumping of nerve roots (axial images) in 57% (12/21), followed by nerve root enhancement (axial images) in 50% (7/14), and cauda equina enhancement (sagittal images) in 42% (6/14). In the CISP-plus cohort, 10 patients had MRI imaging of lumbar (n=8) or brachial plexus (n=2). Abnormal plexus contrast enhancement was seen in 90% (9/10), with thickening of femoral or sciatic nerves, and of the divisions of the brachial or lumbosacral plexus (Figure 7).

Central demyelination and other associations

Six of our cases had concurrent central demyelinating disease (diagnosed as co- existing multiple sclerosis; 3 with CISP-plus and 3 with CISP) with 3 previously reported. One CISP-plus case had longstanding HIV being treated with anti-retroviral therapy. Two patients (one of 4 CISP-plus and one of 6 CISP tested) were positive for contactin-1/CASPR1 antibody confirmed by cell-based assay and immunofluorescence.

Immunotherapy and Clinical outcomes

Forty CISP-plus and 17 CISP patients were treated with immunotherapy. The initial immunotherapy was intravenous immunoglobulins (IVIG) in 80% (32/40) of CISP-
plus and 82% (14/17) of CISP cases. Intravenous methylprednisolone (IVMP) was used initially in 15% (6/40) of CISP-plus and 18% (3/17) in CISP cases. Plasmapheresis (PLEX) and rituximab were each used initially in one CISP-plus case (3%, 1/40). A second immunotherapy was used in 11 CISP-plus (IVMP in 8, IVIG, PLEX and azathioprine each in one) and in 2 CISP cases (PLEX and IVIG each in one). Two CISP-plus cases needed a third immunotherapy: rituximab (1) and PLEX (1).

Treatment response and outcome data was available in 32 CISP-plus and 14 CISP cases and showed clear improvement for the group as a whole. At baseline, all CISP-plus patients had abnormal neurological examinations: 87.5% (28/32) had gait ataxia and 19 used ambulatory aids (11 canes, 5 walkers and 3 wheelchairs). At baseline, all CISP patients had abnormal neurological examinations and 10 used ambulatory aids (6 cases and 4 walker/wheelchair combination). At post-treatment follow-up, 84% (27/32) CISP-plus and 93% (13/14) CISP (p= NS) showed marked improvement of gait ataxia and had reduced numbness and paresthesia. Three of 32 CISP-plus cases were stable and 2/32 worsened. One CISP case was stable and none worsened. Neurological functional outcomes (assessed at final neurological visit) including needing assistance in daily tasks were markedly better after treatment (p<0.001, OR=40.25, CI: 6.5-249.1). Overall, 54% (25/46), 59% (19/32) CISP-plus and 43% (6/14) CISP patients returned to normal neurological examinations. Nine CISP-plus (cane; 7, wheelchair; 2) and 6 CISP patients (cane; 5, scooter; 1) still required ambulatory aids; the need for ambulatory aid was unknown in the rest. Overall for CISP and CISP-plus patients combined, use of ambulatory aids went from 29 at baseline to 15 post-treatment with OR=30 (P<0.001, CI: 6.02-156.08). Two non-related deaths occurred from cancer (1) and liver failure (1) in the CISP-plus cohort.

**Discussion**

Since the original description of CISP we have become aware of patients presenting with a clinical syndrome similar to CISP but in whom the disease extends beyond dorsal roots to also involve motor and postganglionic sensory nerve fibers, resulting in mild distal weakness and mild abnormalities on NCS/EMG (Figure 1A). Knowing how to best classify such patients has been problematic. They cannot correctly
be classified as CISP because their disease is not isolated to the dorsal root and many do not exclusively have sensory symptoms. However, they also do not meet the diagnostic criteria for classical CIDP or sensory CIDP, which require demyelinating abnormalities on NCS.

In our study, we introduce the concept and terminology of CISP-plus by identifying non-pure, sensory predominant, inflammatory polyradiculopathy patients and comparing them to pure-CISP patients. Our intent is to show that CISP-plus and CISP patients are alike. We found striking similarities in the clinical, SSEP, QST, CSF, MRI and pathological features as well as in the treatment response between the CISP-plus and CISP cohorts supporting our belief that they should be classified together. Both groups present with large fiber sensory loss, imbalance, frequent falls and little pain. Use of gait aids is necessary in almost half of the patients in both groups. On examination, both groups have reduced light touch, vibration and proprioception, hypo- or areflexia and gait ataxia. One important difference (that explains why they have been thought of as different conditions) is the presence of weakness, which is distal and lower limb predominant (toe flexor and extensor) in CISP-plus. This degree of weakness is mild and non-disabling, and its clinical relevance in CISP-plus is small; severe gait impairment and profound sensory loss are the main sources of disability in both CISP-plus and CISP patients.

Neurophysiological tests are also similar between groups. SSEP is a very useful diagnostic tool and should be considered in all suspected CISP-plus or CISP cases. Often SSEP slowing is non-localizable (as evidenced by delayed cortical responses) but this confirms that pathology exists somewhere along the somatosensory pathways. The tibial studies are often non-localizable due to the frequent absence of the lumbar spine potential (N22) (location of sensory roots). However, in one-quarter of CISP-plus SSEP studies, the tibial N22 response was preserved and prolonged confirming lumbar root slowing. Furthermore, for many, the median (upper limb) SSEP in both CISP-plus and CISP localizes the slowing to the cervical sensory root level (prolonged N13 or N9-N13 interpeak latencies) indicative of focal root demyelination (Figure 1B). QST results mirror the clinical syndrome and provide evidence that large fiber abnormalities (reduced light touch and vibration) predominate for both CISP-plus and CISP cohorts. As expected, symptoms referable to small myelinated and unmyelinated fibers
(neuropathic pain and autonomic dysfunction) and corresponding abnormalities on QST (reduced cooling and heat pain sensation) and autonomic testing are less common. CSF proteins are at least moderately elevated in the vast majority of both CISP-plus and CISP patients and support an inflammatory root process. MRI of the lumbar spine shows nerve root thickening, clumping and enhancement in more than half of CISP-plus and CISP patients (Figure 7). In addition, there is radiographic evidence of peripheral nerve involvement beyond the root level in CISP-plus patients with most plexus MRI studies being abnormal. The main neurophysiological difference between CISP-plus and CISP is found on NCS/EMG, because CISP by definition excludes NCS/EMG abnormalities whereas CISP-plus allows them. The NCS abnormalities in CISP-plus are mild, do not meet electrophysiological criteria for CIDP in any cases and incorrectly imply that the pathology is axonal predominant. The majority of needle EMG studies in CISP-plus are normal and only rarely show a mild motor polyradiculopathy with distal denervation.

The similarities in nerve pathology observed in the CISP-plus and CISP cohorts are also noteworthy and dorsal lumbar rootlet biopsies are essentially indistinguishable. Both show loss of large myelinated nerve fibers, a resultant unimodal small myelinated fiber size distribution (Figure 4), onion-bulb formations (Figures 4 and 6), increased rates of segmental demyelination (Figure 3) and scattered endoneurial inflammation (Figure 3F-G). Nerve biopsies distal to the dorsal root were not performed in CISP patients at our institution because the disease is restricted to the dorsal root. In contrast, targeted fascicular sciatic and distal cutaneous nerve biopsies were performed in CISP-plus patients and showed similar findings as were found in the rootlet biopsies but of lesser severity (Figure 3, 5 and 6). These are the same pathological findings typically seen in classical CIDP.\(^1\,^2\)

Response to immunotherapy in CISP-plus and CISP patients was also similar with marked improvement of neurological deficits, especially the sensory ataxia. Approximately half of CISP-plus and CISP patients returned to normal neurological examinations including resolution of weakness (in CISP-plus) with treatment (25/46 overall). For all patients, the most widely used immunotherapies were IVIG and IVMP. Many patients with falls and severe imbalance for years still improved with immunotherapy, suggesting that treatment is effective even after many years. The likely
explanation is that ongoing inflammatory demyelination is amenable to delayed treatment whereas axonal degeneration is not.

Recently, some authors have described chronic immune sensorimotor polyradiculopathy (CISMP), a syndrome that shares some features with CISP, including having the pathological process localized to proximal nerve segments, lack of demyelination on NCS, thickened nerve roots on MRI and elevated CSF protein.\textsuperscript{23, 24} The question could be asked of whether CISP-plus patients should be classified as CISMP. We believe that for the cases described here, CISP-plus is a more correct term. Most cases of CISMP have a somewhat different clinical presentation – usually in CISMP there is prominent weakness (especially lower limbs) and less frequent sensory ataxia, whereas weakness is minimal in CISP-plus and sensory ataxia is almost universally present. Consequently, we do not think that CISP-plus cases should be classified as CISMP. However, we acknowledge that these conditions may lie on a continuum and that borderline cases between the two entities exist making classification difficult. Additionally, CISP-plus is a more suitable term to describe our patients as it highlights their sensory and dorsal root predominant presentation and connects them to CISP.

We believe that there is a strong justification to classify CISP-plus and CISP together as sensory variants of CIDP but maintaining the distinction from CISMP and typical sensory CIDP. The evidence is overwhelming that these are forms of inflammatory demyelinating neuropathy primarily localized to dorsal nerve roots. It is likely that CISP-plus and CISP are part of one disease that in some cases is restricted to the sensory nerve root (CISP) while in others extends beyond to involve motor and sensory fibers to a lesser degree (CISP-plus). Furthermore, CISP-plus may be even more important to recognize than CISP, as we found more cases of CISP-plus than CISP during the same time period (although we acknowledge that this is not an epidemiological study).

CISP-plus and CISP are both difficult to recognize and diagnose. The diagnosis of CISP is challenging because despite patients having profound sensory deficits, NCS/EMG are entirely normal, leading to some patients being labeled as hysterical.\textsuperscript{7} Similarly, CISP-plus patients are difficult to diagnose because their NCS/EMG
abnormalities are mild and not severe enough to explain their clinical deficits, they are not in the demyelinating range and they do not meet the EFNS/PNS criteria for CIDP.\textsuperscript{12} In fact, the NCS/EMG findings likely falsely point physicians away from considering an inflammatory demyelinating disorder and towards an axonal pathology. Consequently, the possibility of CIDP is probably not considered by many physicians evaluating CISP-plus patients, which may explain the trend for more delay in diagnosis in CISP-plus vs. CISP patients (Figure 2). It is important for physicians, especially neurologists, to be aware of both conditions so they can recognize and treat them promptly. Both are very responsive to immunotherapy, especially to IVIG, even years after disease onset, and with treatment neurological examinations often return to normal.

We felt it was important to include CISP-plus cases with co-existing infectious or immune-mediated diseases as their clinical features mimicked the rest of the cohort and were not explained by their concomitant disorders. One CISP-plus with longstanding HIV and 6 with concurrent central demyelinating disease (3 CISP-plus and 3 CISP) all had improvement of ataxia with IVIG. Two patients (one CISP and one CISP-plus) were positive for contactin-1 antibodies, which are known to be associated with inflammatory sensory-predominant neuropathies.\textsuperscript{5, 6} Finding co-occurring autoimmune diseases supports our hypothesis that CISP-plus and CISP are immune-mediated neuropathies.

The limitations of our study include being retrospective and not population-based, therefore the frequency of CISP-plus vs. CISP cases may be skewed. Because it is retrospective, patients were evaluated in a non-standardized manner, including the choice of immune-therapy and the treatment follow-up. However many patients received comprehensive and uniform evaluations because they were personally seen by two of the authors (PJBD or CJK).

Herein we introduce the syndrome of CISP-plus. CISP-plus is very similar to CISP and both present with sensory loss and sensory ataxia; they differ in that CISP-plus is not completely isolated to the dorsal nerve root and there often is slight distal weakness and mild NCS/EMG abnormalities. We propose that CISP-plus and CISP are two similar subtypes of the same disorder and that the diagnostic criteria used to diagnosis CISP cases have incorrectly excluded CISP-plus cases. We argue that CISP-plus and CISP are both atypical subtypes of CIDP and are responsive to
immunotherapy, and that CISP-plus should be included in the spectrum of sensory predominant CIDP.
Figure legends:

Figure 1:

Title: Anatomical and somatosensory localization of pathophysiology in CISP and CISP-plus.

Legend: (A) Anatomical pictorial representation of the nerves affected in (A.a) chronic immune sensory polyradiculopathy (CISP, isolated sensory root involvement) and in (A.b) CISP-plus (primarily but not solely sensory root involvement). The dark shaded area represents the dorsal root where the primary pathology occurs in both conditions and the dotted area represents lesser involvement of other nerves (shown are ventral root, dorsal root ganglion and spinal nerve) that occurs in CISP-plus but not in CISP. (B) Median nerve somatosensory evoked potential (SSEP) tracings from CISP (B.a) and CISP-plus (B.b) patients showing examples where slowing occurs before the cervical spine site (N13) and within the segment between the clavicular and cervical spine sites (N9 – N13, the segment containing the sensory root). The absolute and inter-peak latencies values (in milliseconds) from the median SSEP studies as well as the normal values are listed at the bottom. These SSEP findings show that the slowing in both conditions primarily occurs at the sensory root level.
A.a  Pure – CISP

B.a

N5
N9
N13
N20
N35

Clavical N9  11.1
Cervical N13  17.3
Cortical N20  23.6
N9 – N13  8.1
N9 – N20  13.0

A.b  CISP – Plus

B.b

N5
N9
N13
N20
N35

11.7  (8.2–11.7 ms)
16.9  (11.3–15.5 ms)
22.1  (16.9–21.9 ms)
5.2  (2.2–4.7 ms)
10.5  (7.8–10.5 ms)
Figure 2
Title: Diagnosis delay in patients with CISP and CISP-plus

Legend: Time to diagnosis plots comparing chronic immune sensory polyradiculopathy (CISP) to CISP-plus patients showing that both groups have delayed diagnoses and that 12 patients from both groups were diagnosed > 10 years after symptom onset (to the right of the dotted line). The trend to a more delayed diagnosis in CISP-plus compared to CISP (p=0.06) may be due to the nerve conduction findings being more in keeping with axonal and not demyelinating pathology in CISP-plus patients. Such findings may wrongly point physicians away from an inflammatory demyelinating neuropathy in CISP-plus patients.
Figure 3
Title: Segmental demyelination on teased fiber preparations in CISP-plus

Legend: Teased myelinated nerve fiber preparations from patients with chronic immune sensory polyradiculopathy plus (CISP-plus) taken from proximal and distal nerves showing chronic demyelination and remyelination at different stages and severities. (A), (B) Dorsal rootlet biopsies showing onion-bulb formations (thickened strands of multiple Schwann cell processes surrounding nerve fibers). (C) Fascicular sciatic biopsy and (D) sural biopsy showing areas of ongoing demyelination and remyelination. (E) Sural biopsy demonstrating myelin reduplication (small tomaculae; thickened areas of myelin along the lengths of nerve fibers). (F), (G) Serial longitudinal paraffin sections of a CISP-plus biopsy showing abnormal amounts of scattered endoneurial inflammation on H&E (F) and CD45 (G) preparations. The teased fiber changes show that in CISP-plus ongoing chronic demyelination and remyelination occurs at multiple nerve levels but are the most severe in the sensory roots.
Figure 4
Title: Loss of large myelinated fibers and onion-bulbs in dorsal lumbar rootlets of CISP-plus

Legend: Dorsal lumbar rootlet biopsies (A.a, B.a, C.a, D.a) and their corresponding myelinated fiber histograms (A.b, B.b, C.b, D.b) from a normal control (A) and from three patients with chronic immune sensory polyradiculopathy plus, CISP-plus (B), (C) and (D). The sections are methylene blue stained epoxy preparations. The control biopsy (A) and histogram shows a normal bi-modal size distribution. The CISP-plus biopsies are arranged in order from least (B) to most severely (D) affected. Note that in all three CISP-plus rootlet biopsies, the density of myelinated fibers is preserved but the size distribution is altered with loss of large myelinated fibers and a relative increase in the number of small myelinated fibers. These findings are confirmed in the histograms with loss of large myelinated fiber peaks (at 8.5 um on the control) and larger amplitudes of the small myelinated fiber peak (at 3.0 um). Note the frequent onion-bulbs (arrowheads) as well as the demyelinated axons surrounded by onion-bulbs (arrows) in (C) and (D). The loss of large myelinated sensory fibers demonstrated here correlates well with the clinical syndrome of gait ataxia. The severe pathological findings from dorsal roots in CISP-plus are similar to those found in CISP rootlet biopsies. Morphometric analysis showed the mean MF density (MF/mm²) of 3 dorsal rootlet in CISP-plus was 16,556/mm² (SD +/− 5,917/mm²) and was similar to the densities of CISP and controls dorsal root biopsies. Individual densities were: (B) 21,218, (C) 18,552 and (D) 9,899/mm². The 3 normal dorsal rootlet control biopsies had a mean MF density of 16,700/mm² (SD +/− 1,200/mm²) and 3 CISP dorsal rootlet biopsies had a mean MF density of 14,300/mm² (SD +/− 1,850/mm²).
Figure 5
Title: Loss of large myelinated fibers and onion-bulbs in limb nerves of CISP-plus
Legend: Nerve biopsies (A.a, B.a, C.a, D.a) taken from proximal and distal limb nerves from a normal control (A) and from three patients with chronic immune sensory polyradiculopathy plus, CISP-plus (B-D) and their corresponding myelinated fiber histograms (A.b, B.b, C.b, D.b). The biopsies are methylene blue stained epoxy sections. All CISP-plus biopsies have reduced numbers of large myelinated fibers and a unimodal size distribution with a small fiber peak at about 3.5 um on the histograms. (A) Normal control sural nerve shows normal myelinated fiber density and bimodal size distribution (with peaks at 3.5 um and 9 um). CISP-plus biopsies of sural (B) and superficial radial nerves (C), showing increased regenerating nerve clusters in (C) (arrowheads). (D) CISP-plus fascicular sciatic nerve biopsy showing occasional onion-bulb formations (arrows). The CISP-plus nerve biopsies demonstrate that large myelinated fiber loss and onion-bulb formation are not restricted to the sensory root level (as in CISP) but extend to more distal nerves to a lesser degree. Morphological analysis for 2 fascicular sciatic biopsies, showed the mean MF density was 6,656/mm² (6,742 and 6,570/mm²), for the superficial radial biopsy the MF density was 9,153/mm² and for 5 sural nerve biopsies the mean MF density was 5,724/mm² (SD +/- 1864/mm²). Individual sural densities were: 4,107; 4,413; 5,114; 6,280 and 8,706/mm²; 4 of the sural nerves were mildly reduced (4,000 to 6,500/mm²) and 1 was normal (6,500 to 13,000/mm²) per our laboratory MF density values.
Figure 6
Title: Onion-bulb formation on electron microscopy in CISP-plus

Legend: Electron micrographs taken from different nerves of patients with chronic immune sensory polyradiculopathy plus (CISP-plus) showing evidence of chronic demyelination and abortive repair. The left column is at low magnification and the right column is at high magnification. (A), (B) Dorsal lumbar rootlet biopsy showing frequent large onion-bulbs. (C), (D) Fascicular sciatic nerve biopsy showing frequent but smaller onion-bulbs than were found in the dorsal roots. (E), (F) Superficial radial nerve biopsy showing frequent regenerating nerve clusters. (G), (H) Sural nerve biopsy showing rare small onion-bulbs. The chronic demyelinating changes occur at all levels but are most frequent and severe in proximal nerves (especially at the sensory root level).
Figure 7
Title: MRI abnormalities in CISP-plus
Legend: (A) T2 axial lumbar MRI from a patient with chronic immune sensory polyradiculopathy plus (CISP-plus) showing clumping and thickening of lumbar nerve roots. (B) The same patient and lumbar level as in (A) with T1 post-contrast imaging showing contrast enhancement of the roots. (C) Sagittal T1 post contrast imaging of the cauda equina from a patient with CISP-plus showing enlargement and enhancement of the lumbar roots. (D) T2 axial MRI of the lumbosacral plexus from a patient with CISP-plus showing enlarged nerves with increased T2 signal of the lumbosacral plexus on the right (arrow) compared to the left.
References

## Appendix. Authors

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