Received: 28 April 2020 | Revised: 23 December 2020 | Accepted: 15 January 2021

DOI: 10.1111/jns.12433

RESEARCH REPORT

WILEY

Sensory neuronopathies: A case series and literature review

Agustin Sancho Saldaña[1,2] | Mohamed Mahdi-Rogers[1] | Robert David Hadden[1]

[1]Department of Neurology, King's College Hospital NHS Foundation Trust, Denmark Hill, London, UK

[2]Department of Neurology, Hospital Universitario Miguel Servet, Zaragoza, Spain

Correspondence
Agustin Sancho Saldaña, Department of Neurology, Institution: King's College Hospital NHS Foundation Trust, Denmark Hill, London SE5 9RS, UK.
Email: agustinsanchosaldana@gmail.com

Abstract

Sensory neuronopathies are heterogeneous disorders of dorsal root ganglia. The clinical and laboratory features in a single-centre series, including response to treatment and outcome have been described. They retrospectively included 54 patients meeting Camdessanché et al (2009) criteria for sensory neuronopathy. The patients were classified according to their likely aetiology and analysed their demographic, clinical, neurophysiological, histological and spinal MRI features. The outcome with the modified Rankin Scale (mRS) was evaluated, and the response to treatment was assessed. About 54 patients were included (18 male; median age 54.5 years). The most common initial symptoms were hypoaesthesia, paraesthesia, ataxia and pain. Half of patients had a slow onset, greater than 12 months before seeing a neurologist. The aetiology as possibly inflammatory (meaning nonspecific laboratory evidence of immune abnormality) in 18 patients (33%), paraneoplastic 8 (15%), autoimmune 7 (13%) and idiopathic 6 (11%) was classified. About 31 patients received immune therapy of which 11 (35%) improved or stabilised. Corticosteroids were the most used treatment (24 patients) and cyclophosphamide had the highest response rate (3/6, 50%). At the final follow up (median 24 months) 67% had mRS ≥3 and 46% mRS ≥4, including 15% who died. Worse outcome was associated with generalised areflexia and pseudoathetosis by logistic regression, and with motor involvement and raised CSF protein by univariate analysis. Sensory neuronopathies caused severe disability, especially in patients with generalised areflexia and pseudoathetosis. Of those without an obvious cause, most had some evidence of dysimmunity. Some patients had a positive response to immunotherapy, but rarely enough to improve disability much.

KEYWORDS
ataxic neuropathy, disability, ganglionopathy, immunotherapy, inflammation, sensory neuron disease, sensory neuronopathy

1 | INTRODUCTION

Sensory neuronopathies (SNN), also known as sensory neuron diseases or sensory ganglionopathies, are an uncommon specific subgroup of peripheral nervous system diseases characterised by primary pathology of sensory neurons in dorsal root ganglia,[1,2] causing degeneration of both their central and peripheral sensory axons.[3] Differentiating these from other peripheral diseases such as polyneuropathies is important, since SNN may need specific investigations and treatments because of their frequent association with paraneoplastic and dysimmune disorders, toxins, vitamin-related damage and more rarely with infective or genetic disorders.[1-5] Although in about 50% of patients with SNN the disease is idiopathic,[1,6] pathological examination of dorsal ganglia showed inflammatory T-cell reaction along with degeneration, suggesting that it might be driven by a cell mediated immune response.[7,8] Definitive diagnosis requires biopsy of dorsal

root ganglia, but this is technically difficult and therefore not recommended. In the 1980s, Asbury[9] proposed that a non-length dependent sensory loss and an almost pure and severe electrophysiological sensory involvement were the hallmark of SNN, but it was not until 2009 when Camdessanché[10] proposed diagnostic criteria applicable in routine clinical care, relying on clinical and neurophysiological examination to diagnose SNN. These criteria were later validated in a multicentre study.[11]

There have been no blinded, placebo-controlled, clinical trials investigating the best treatment of SNN so clinical practice is informed by isolated case reports or small case series. We describe clinical, neurophysiological, histological and spinal MRI features in a series of patients with SNN, and their response to treatment and outcome.

2 | PATIENTS AND METHODS

We retrospectively reviewed data of patients seen in our peripheral nerve clinic over 13 years (from 2006 to 2019). We searched the electronic patient record of King´s College Hospital, London, for the terms 'ganglionopathy' or 'neuronopathy', and we included in our study all patients meeting the Camdessanché criteria for 'possible' or 'probable' SNN.[10] Data were extracted from electronic medical records. All patients included in our study were personally assessed at least once by a neurologist specialised in peripheral nerve.

We excluded patients with demyelinating neuropathy, the ataxic form of chronic inflammatory demyelinating polyneuropathy, anti-MAG neuropathy, CANOMAD or residual sensory ataxia from Guillain-Barré syndrome. Patients diagnosed with pure small fibre ganglionopathy[12] were also excluded since these did not fulfil the Camdessanché criteria and the primary degeneration of dorsal ganglia has not been pathologically demonstrated in this condition.[10]

2.1 | Data recorded for the study

The following data were recorded and analysed: sex and age of onset; relevant medication and comorbidities; clinical information including: clinical course from symptom onset until first assessment by a neurologist (acute, ≤1 month; subacute, >1 month and ≤6 months; subacute-chronic, >6 months and ≤1 year; and chronic, >1 year); symptoms at onset and at full development of the disease; presence of generalised areflexia at full development; distribution of symptoms and asymmetry of symptoms at onset and at full development. The distribution of sensory involvement was classified as consistent or not with a length-dependent pattern. Presence of motor symptoms was also recorded.

Investigations were done at the discretion of the treating neurologist with no formal protocol. We analysed the results of radiological, haematological, biochemical and serological screening to investigate different aetiologies associated with SNN. Cerebrospinal fluid (CSF) analysis abnormalities included protein concentration, presence of pleocytosis or oligoclonal bands. CSF protein level was considered to be raised if >0.45 g/L when less than 60 years old, and >0.6 g/L when more than 60 years old.[13] Spine MRI when available was analysed for signal abnormality in the posterior columns.

Electrophysiological study was analysed to assess the inclusion criteria. We specifically recorded presence of ≥2 sensory action potential (SAP) absent in upper limbs, absence of radial SAP or SAP amplitude <30% of the lower limit of normal, and motor nerve abnormalities.

We classified patients according to the likely aetiology: *paraneoplastic*, if onconeural antibodies were detected or a cancer associated within 5 years of the symptoms[14]; *autoimmune*, if diagnosed with a systemic autoimmune disease associated with SNN (Sjögren's syndrome [SS], systemic lupus erythematosus, celiac disease or autoimmune hepatitis); *infective*, if associated with any infectious disease (HIV, EBV, VZV, HTLV-1, enterovirus, etc); *toxic*, if temporally related to a neurotoxic drug (carboplatin, oxaliplatin, doxorubicin, suramin sodium, bortezomib, thallium, pyridoxine, etc); *nutritional-metabolic*, if temporally related to a vitamin deficiency or metabolic disturbance; *genetic* if a definite pathogenic genetic mutation; or *CANVAS* if a clinical diagnosis of cerebellar ataxia, neuropathy and vestibular areflexia syndrome (not confirmed by genetic testing). We classified patients as *possibly inflammatory* if they met none of the above criteria but had some laboratory or clinical evidence of a possible immune-mediated aetiology (other systemic autoimmune disease not typically related to SNN, raised protein or unmatched oligoclonal bands in CSF, serum autoantibodies, raised inflammatory markers, monoclonal gammopathy, inflammation on sural nerve biopsy or response to immunosuppressive treatment); or *idiopathic* if they met none of the above criteria.

In some analyses we grouped these categories into four groups of aetiologies according to expected natural history and treatment:

1. *Paraneoplastic*: Well defined; treatment and outcome largely related to the cancer.
2. *Autoimmune/idiopathic* (including autoimmune, possibly inflammatory and idiopathic categories): Potentially responsive to immune treatment but mechanism not well understood.
3. *Toxic/nutritional/infective*: Usually monophasic and potentially treatable by non-immune treatment.
4. *CANVAS/ genetic*: Usually slowly progressive and untreatable

2.2 | Follow-up and outcome

Activity limitation was evaluated using the modified Rankin Scale (mRS) at the beginning and end of the follow up, assessed retrospectively from information given in the clinical notes and letters. A poor outcome was defined as mRS ≥3 and very poor outcome as mRS ≥4. Time of follow up since the patient was first seen by a neurologist was also recorded.

Treatment response was classified as 'improvement', 'stability', 'no significant benefit' or 'worsening'. Improvement was defined as

any clinically significant improvement (sustained for at least 3 months) in patient symptoms or in neurological examination verified by a neurologist. Patients who stopped deteriorating were classified as 'stability'. 'No significant benefit' was used for patients who continued worsening at the same speed as before. 'Worsening' was defined as worsening faster than before. A positive treatment response was defined as improvement or stability. Other outcomes were recorded as negative response.

For patients who received immunotherapy, the time between onset of symptoms and first treatment was noted and correlated with the response to treatment.

2.3 | Statistics

Statistical analysis was performed using SPSS 2.0 software. Continuous data was expressed as the mean ± SD, and binary data was given as percentages. The Chi-square test was used for binary data and the Mann-Whitney *U* test for continuous data. $P < .05$ was considered statistically significant. Binary logistic regression was used to predict outcome. Variables included in the model were those with $P < .05$ in the univariate analysis and also the main aetiological groups. High CSF protein was excluded from the logistic regression, although significant in the univariate analysis, because only 34 patients had had a lumbar puncture.

3 | RESULTS

3.1 | Patient characteristics

Of 131 patients identified by our search strategy between June 2006 and September 2019, we included 54 patients who fulfilled our inclusion criteria. About 36 (67%) were female and 18 (33%) male. Using the Camdessanché criteria,[10] 18 (33%) patients were classified as 'probable', 36 (66%) as 'possible' and none as 'definite' SNN. Median age at onset of SNN was 54.5 years old (42-66.5). About 10 patients (18%) had a malignancy and 11 (20%) any associated autoimmune disease. Three patients (6%) had monoclonal gammopathy without underlying malignancy (one IgA kappa and two IgG kappa). About 27 patients (50%) had a chronic onset (Table 1).

We classified the likely aetiology as *paraneoplastic* in 8 (15%) patients. Three were anti-Hu seropositive (one with bronchial carcinoma, one with metastatic neuroendocrine tumour and one with ovarian teratoma although the tumour histology lacked anti-Hu immunoreactivity). Two had an anti-Ma2/Ta antibody (one with bladder carcinoma and the other died before PET-CT). In three patients we did not find onconeuronal antibodies (one had metastatic melanoma, one breast cancer, and one bladder carcinoma). Three patients with antecedent malignancy were not considered to have paraneoplastic SNN. We considered one as autoimmune SNN due to graft versus host disease following bone marrow transplant for leukaemia, one as toxic SNN due to chemotherapy for leukaemia, and one as possibly inflammatory due to non-pulmonary sarcoidosis, because her melanoma had been in remission for 10 years. An *autoimmune* cause was likely in 7 (13%) patients (four Sjögren's syndrome, one SLE, one celiac disease, and one graft vs host disease). Five (9%) had a likely *toxic* cause (two cisplatin, one cytarabine, one amiodarone, one alcohol and one other chemotherapies). Two (4%) patients had an *infective* cause (one VZV and one Lyme disease). Four patients were classified as *nutritional-metabolic*. One (2%) patient had a *genetic* cause (POLG mutation) and 3 patients had *CANVAS*. About 18 patients were classified as *possibly inflammatory*, of which 2/18 (11%) had a systemic autoimmune disease not typically associated with SNN (non-pulmonary sarcoidosis and giant cell arteritis), 5/13 (38%) had high CSF protein, 5/15 (33%) had inflammation on nerve biopsy, 7/18 (38%) had a serum autoantibody (such as anti-Ro without Sjogren's syndrome or dry eyes/mouth, antimitochondrial antibody, ANCA, antinuclear antibody [≥1/160], etc) or abnormal inflammatory marker (including monoclonal gammopathy) and 8/15 (53%) had a positive response to immunotherapy. Two patients that would otherwise have been classified as idiopathic (with no laboratory evidence of dysimmunity) clearly improved after immune treatment, and therefore

TABLE 1 Patient characteristics (n = 54)

	n (%)
Male sex	18 (33)
Age of onset, median (range), years	54 (42–66)
Comorbidities	
Statin intake	7/53 (13)
Diabetes mellitus	5 (9)
Excessive alcohol intake	9 (17)
Smoker	7 (13)
B12 deficiency	3/53 (6)
Malignancy	10 (18)
Autoimmune disease	11 (20)
Monoclonal gammopathy	3 (6)
Clinical course (n = 53)	
Acute	7 (13)
Subacute	11 (21)
Subacute-chronic	8 (15)
Chronic	27 (51)
Aetiology	
Paraneoplastic	8 (15)
Autoimmune	7 (13)
Possibly inflammatory	18 (33)
Idiopathic	6 (11)
Infective	2 (4)
Toxic	5 (9)
Nutritional-metabolic	4 (7)
CANVAS	3(6)
Genetic	1 (2)

Abbreviation: CANVAS, cerebellar ataxia, neuropathy and vestibular areflexia syndrome.

were classified as possibly inflammatory. Finally six patients were *idiopathic*.

In the four grouped aetiologies, we classified 8 (15%) patients as paraneoplastic, 31 (57%) patients as autoimmune/idiopathic, 11 (20%) patients as toxic/nutritional/infective and 4 (7%) patients as CANVAS/genetic. Patient characteristics (age, sex and comorbidities) did not differ significantly across the four aetiological groups (Table 1).

3.2 | Symptoms

The most common findings at onset were hypoaesthesia, paraesthesia, ataxia and pain (Table 2). At full development hypoaesthesia (99%) and ataxia (94%) were by far the most common symptoms. Paraesthesia was the only symptom more common at onset (51%) than at full development (44%). Motor involvement was found in 28% of patients. Symptoms started in upper limbs in 43% of patients, in lower limbs in 40% and in four limbs in 19% of patients. Symptoms were asymmetrical in 37% of patients at onset, in 48% at full development and in 65% at any time. Symptoms had a non-length dependent distribution in 80% of patients. Other symptoms and signs are summarised in Table 2.

Comparing the four groups of aetiologies, the paraneoplastic group had more motor involvement [5/8 (62.5%) vs (10/46) 22%, P = .03]. Patients from the autoimmune/idiopathic group tended to have more bladder dysfunction at full development [5/31(16%) vs 0/23 (0%), P = .054 NS]. The toxic/nutritional/infective group less frequently had asymmetric distribution at any time [4/11(36%) vs 31/43 (72%), P = .033], more frequently presented with abnormality of all limbs at onset [5/10(50%) vs 5/43 (12%), P = .014), and less frequently presented with a chronic course [2/11(18%) vs 25/43(58%), P = .020]. Patients in the CANVAS/Genetic group had more vestibular involvement [3/4(75%) vs 2/50 (4%), P = .02], more neurogenic cough [2/3(67%) vs 4/50(8%), P = .031], more eye movement involvement [4/4 (100%) vs 4/50 (8%), P < .001], and more frequently a chronic course [4/4 (100%) vs 23/50 (46%), P = .055 NS]. Other symptoms did not differ significantly across the four aetiological groups.

3.3 | Laboratory findings

The radial sensory potential was absent or ≤30% of LLN in 76% of patients. Sural nerve biopsy was performed in 28 patients and all showed axonal loss. About 7 (25%) nerve biopsies had mild non-specific inflammatory cells and 6 (21%) had some regeneration. Spinal MRI was performed in 36 patients of which 6 (17%) revealed high intensity in cervical dorsal columns. CSF was obtained in 34 patients, 11 (32%) of which showed raised protein. Other findings are summarised in Table 3. Laboratory findings did not differ significantly across the four aetiological groups.

3.4 | Treatments and outcome

Immune therapy was used in 33 patients but we had follow-up data to determine the response in only 31 patients. Table 4 summarises

TABLE 2 Symptoms

Symptoms n (%), n = 53	At onset	At full development	At any time
Pain	17 (32)	32 (59)	
Hypoaesthesia	36 (68)	53 (99)	
Paraesthesia	27 (51)	24 (44)	
Ataxia	17 (32)	51 (94)	
Pseudoathetosis	0 (0)	12 (22)	
Dry eyes and mouth[a]	4 (7)	11 (20)	
Autonomic symptoms	10 (19)	14/52 (27)	
Orthostatic hypotension	4 (7)	6 (11)	
Gastrointestinal dysfunction	4 (7)	8 (15)	
Dysphagia	2 (4)	5 (9)	
Erectile dysfunction	1 (2)	2 (4)	
Bladder dysfunction	0 (0)	5 (9)	
Sweating dysfunction	1 (2)	4 (7)	
Pupil abnormalities	1 (2)	3/53 (6)	
Vestibular dysfunction			5 (9)
Cough			6/53 (11)
Facial involvement			11 (20)
Motor involvement			15 (28)
Eye movement abnormalities			8 (15)
Generalised areflexia			28/52 (54)

[a]One patient took gabapentin and one fluoxetine.

TABLE 3 Laboratory findings

	n abnormal/tested (%)
Nerve conduction testing	
≥2 SAP absent in upper limbs	39/50 (78)
Radial SAP absent or <30% of LLN	28/37 (76)
All motor potentials normal	37/53 (70)
Sural nerve biopsy (n = 28)	
Axonal loss	28 (100)
Inflammation	7 (25)
Regeneration	6 (21)
Demyelination	0 (0)
MRI spine	
T2 hyperintensity dorsal columns	6/36 (17)
Dorsal root enhancement	1[a]
CSF (n = 34)	
Pleocytosis	0 (0)
Raised protein	11 (32)
Unmatched OCB	1 (3)

Abbreviations: CSF, cerebrospinal fluid; LLN, lower limit of normal; MRI, magnetic resonance imaging; OCB, oligoclonal bands; SAP, sensory action potential.
[a]One patient had dorsal root enhancement but we have no data on how many patients were given contrast.

the response to immune therapy. Corticosteroids were the most used immune therapy with a response (improvement or stabilisation) in 6/24 (25%) patients. Cyclophosphamide had the highest response rate, in 3/6 (50%) patients. Among 11 patients who responded to immunotherapy, 7 improved by 1 mRS point (none by more) and 4 stabilised. In the autoimmune/idiopathic group, of 8 patients who received immune therapy during the first year after symptom onset, 6 (75%) responded to treatment, compared with 2 (15%) responders in 13 patients starting treatment later than 1 year (P = .06, NS). The only patient who improved by 2 mRS points had nutritional-metabolic aetiology, treated with vitamins.

Median follow up was 24 (interquartile range 12-36) months from the time of first seeing a neurologist. At the final follow up, 36 (67%) had a poor outcome (mRS ≥3), of which 25 patients (46%) had very poor outcome (mRS ≥4) including 8 patients who died (15%). Figure 1 summarises the change in mRS between the beginning and end of follow up.

Cause of death in four patients with paraneoplastic SNN was related to the underlying tumour. One patient (autoimmune group) died due to neutropenic sepsis secondary to immunosuppressive therapy for graft versus host disease after bone marrow transplant. One patient with POLG mutation died from status epilepticus. One patient (toxic group) transiently responded positively after stopping chemotherapy but died 5 months later from bronchopneumonia. One patient with *possibly inflammatory* SNN died due to subdural haematoma after a fall.

TABLE 4 Neurological response to immune treatments or cancer treatment according to aetiology

Aetiological group	Treatment	Total patients receiving each treatment[a]	Positive response		No response	Inadequate trial or not tolerated
			Improvement	Stabilisation		
Paraneoplastic	Corticosteroid	2	1 (50%)	0	1 (50%)	0
	IVIg	1	0	0	1 (100%)	0
	Azathioprine	1	0	0	1 (100%)	0
	Cyclophosphamide	2	1 (50%)	0	1 (50%)	0
	Cancer treatment	4	0	2 (50%)	1 (25%)	1 (25%)
Autoimmune/idiopathic[b]	Corticosteroid	19	2 (10%)	3 (16%)	12 (63%)	2 (10%)
	IVIg	13	3 (23%)	0	10 (77%)	0
	Plasma exchange	5	1 (20%)	0	3 (60%)	1 (20%)
	Azathioprine	2	1 (50%)	0	1 (50%)	
	Mycophenolate mofetil	7	0	0	3 (43%)	4 (57%)
	Cyclophosphamide	4	2 (50%)	0	1 (25%)	1 (25%)
	Any immune treatment	23	7 (30%)	4 (17%)	11 (48%)	1 (4%)
Toxic/nutritional/ infective	Corticosteroid	2	0	0	2 (100%)	0
	IVIg	1	0	0	0	1 (100%)
CANVAS/genetic	Corticosteroid	1	0	0	1 (100%)	0

Abbreviation: IVIg, intravenous immunoglobulin.
[a]Patients who received more than one type of immune treatment are listed in this table more than once.
[b]The proportion responding to any immune treatment was 2/6 patients (33%) with autoimmune aetiology, 9/15 (60%) with possibly inflammatory aetiology and 0/2 (0%) with idiopathic aetiology.

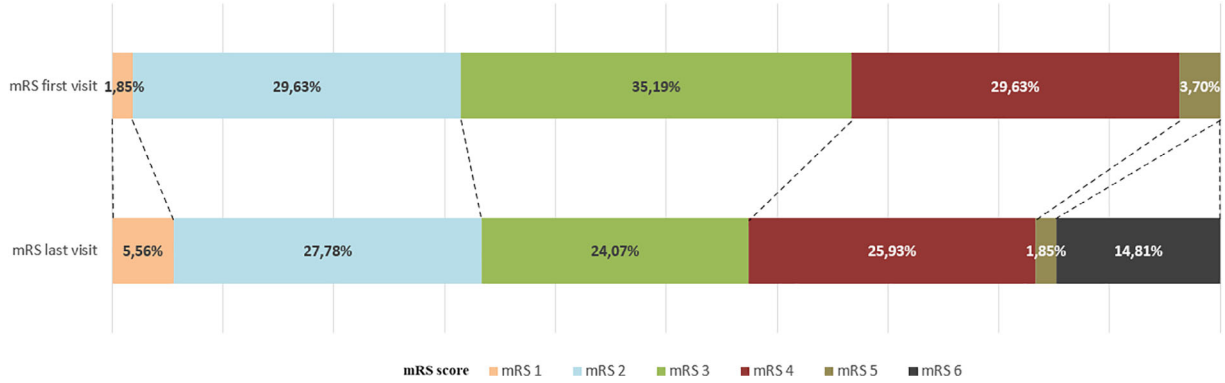

FIGURE 1 Activity limitation (modified Rankin Scale) when first seen by a neurologist and at final follow-up

TABLE 5 Factors associated with very poor outcome (mRS ≥4) (Univariate analysis)

Factor	Total patients with factor	Very poor outcome when factor present	Very poor outcome when factor absent	*P*
High CSF protein	11/34	9/11 (82%)	9/23 (39%)	.023
Generalised areflexia	28/52	19/28 (68%)	3/24 (12%)	<.001
Pseudoathetosis	12/54	10/12 (83%)	14/42 (33%)	.003
Motor involvement	15/54	11/15 (73%)	13/39 (33%)	.009
Paraneoplastic group	8/54	6/8 (75%)	18/46 (39%)	.067
Autoimmune/idiopathic group	31/54	14/31 (45%)	10/23 (43%)	.56
Toxic/nutritional/infective group	11/54	2/11 (18%)	22/43 (51%)	.049
Genetic/CANVAS group	4/54	2/4 (50%)	22/50 (44%)	.6

Abbreviations: CSF, cerebrospinal fluid; mRS, modified Rankin Scale.

TABLE 6 Factors associated with very poor outcome (Logistic regression)

	OR	95% CI	*P*
Pseudoathetosis	61.6	3-1249	.007
Generalised areflexia	31.8	2.7-369.7	.006
Paraneoplastic group	12.1	0.2-834	.25
Motor involvement	3.3	0.4-28	.26
Autoimmune/idiopathic group	1.04	0.05-20	.98
Toxic/nutritional/infective group	0.05	0.01-3.7	.17

A very poor outcome was associated with generalised areflexia and pseudoathetosis (at any time) by logistic regression, and also with motor involvement and raised CSF protein by univariate analysis (Tables 5 and 6). There was a good outcome (mRS ≤2) in 5/6 (83%) patients with regeneration on nerve biopsy compared with 1/5 (17%) without regeneration (P = .003).

3.5 | Outcome related to aetiology

The outcome according to aetiology is summarised in Table 7. In patients with neurological improvement or stabilisation, this was maintained until final follow-up in all, except three patients who later worsened and one who later died of cancer without neurological deterioration. More information about every patient's aetiology, outcome and time of follow-up is summarised in Supporting Information.

The paraneoplastic group was associated with poor outcome and with death [4/8(50%) vs 4/46 (9%), P = .012]. Within the paraneoplastic group, a very poor outcome was associated with non-length dependent distribution and asymmetry [6/6(100%) vs 0/2(0%), P = .036]. Within the autoimmune/idiopathic group, a very poor outcome was associated with generalised areflexia [12/17 (71%) vs 2/14(14%), P = .002], pseudoathetosis at any time [7/8 (87%) vs 7/23 (30%), P = .008] and ataxia at onset [7/9 (78%) vs 7/22 (32%), P = .026]. Patients in the autoimmune/idiopathic group possibly had an increased risk of death [2/8(25%) vs 6/46(13%), P = .053 NS]. The toxic/nutritional/infective group was less likely to have a very poor outcome. Within the toxic/nutritional/infective group, very poor outcome was associated with pseudoathetosis at any time [2/3(67%) vs 0/8(0%), P = .055 NS]. Within the CANVAS/genetic group, we found no factor associated with worse outcome.

4 | DISCUSSION

Our study aimed to be a clinically practical description of the final diagnoses, treatments and outcomes of a syndrome defined clinically

TABLE 7 Outcome at final follow-up, according to aetiology

Aetiology (n)	Improved		Stabilised		Initially improved or stabilised, then later worsened		Worsened		No follow up		mRS at final follow up, median (IQR)
	n	%	n	%	n	%	n	%	n	%	
Paraneoplastic[8]	1	12	0	0	2[a,b]	25	4[c]	50	1	12	5 (3.25-6)
Autoimmune[7]	1	14	1[d]	14	1[a]	14	3	43	1	14	3.5 (2-4.75)
Possibly inflammatory[18]	4	22	4	22	1[a]	5	9	50	0	0	3 (2–4)
Idiopathic[6]	0	0	1	17	0	0	4	67	1	17	3.5 (2.5-4)
Infective[2]	0	0	2	100	0	0	0	0	0	0	2.5 (2-3)
Toxic[5]	2	40	2	40	0	0	0	0	1[a]	20	3 (1-4.5)
Nutritional-metabolic[4]	1	25	0	0	0	0	3	75	0	0	2 (2-2.75)
CANVAS[3]	0	0	0	0	0	0	2	67	1	33	2 (2–2)
Genetic[1]	0	0	0	0	0	0	1[a]	100	0	0	6 (6-6)
Total (54)	9	17	10	18	4	7	26	48	5	5	3(2-4)

[a]One patient died.
[b]Died of cancer without neurological worsening.
[c]Three patients died.
[d]The patient with autoimmune SNN who stabilised had coeliac disease and the treatment was gluten-free diet.

using readily available tests. In the absence of definitive proof of dorsal root ganglia (DRG) involvement (biopsy is clinically impractical) or other gold standard, we used the current validated criteria to define possible SNN in our series.[10] Therefore some of our patients may actually have had a non-length dependent sensory axonopathy rather than neuronopathy.

SNN are characterised by primary pathology of sensory neurons in the DRG. Capillaries supplying DRG are fenestrated giving a deficient blood-nerve barrier which makes DRG more vulnerable to insults such as toxins or antibodies.[1,15] Primary damage of DRG, with an inflammatory T-cell reaction, has been demonstrated pathologically in humans and animal models of different aetiologies[7,15-22]. The term small fibre ganglionopathy is sometimes used to describe a non-length dependent pattern of small fibre symptoms in which pathology may be localised to small fibre neurons in the DRG,[12] but this has not been pathologically proved.

There are two groups of neurons in DRG: large-light cells which are the origin of Aβ and Aδ fibres, and small-dark cells, from which C fibres arise and represent 60%-70% of DRG neurons.[18,19] Degeneration of DRG causes a mixture of large-fibre and small-fibre symptoms in different proportions. In our study, ataxia was present in 32% of patients at onset and 94% at full development, which was the main cause of disability. Hypoesthesia was the most common sign both at onset and full development. Pain, caused by degeneration of small neurons was the third most common symptom. Autonomic symptoms were reported in 19% of our patients at onset and 27% at full development, similar to previously published series.[10] Pseudoathetosis is caused by severe loss of proprioception[20] present in 22% of patients at full development. We found eye movement disorders, such as nystagmus, in 15% of patients, which may be caused by deafferentation of the external ocular muscles or the vestibular system.[1,6] Vestibular involvement was reported in 9% of cases. This is especially relevant in CANVAS in which bilateral vestibular hypofunction is a key feature in the diagnosis.[21] Motor involvement occurred in 28% of our patients. This can have different causes: In some cases the disease might not be confined to DRG and can involve motor axons or neurons, especially in Paraneoplastic SNN.[14,22] Another cause can be the inability to maintain a constant motor output due to impaired sensory feedback,[23] called 'pseudoparesis' which is included in the sensory ataxic rating scale, recently validated for patients with SNN.[24] Finally, patients' strength can be affected by deconditioning due to immobility.

Symptoms classically follow a non-length dependent distribution. Almost 90% of our patients had a non-length dependent pattern, which is unlikely in other ataxic peripheral neuropathies, although sometimes differential diagnosis is challenging since diffuse involvement of DRG may mimic a length-dependent distribution, and simultaneous damage of DRG and peripheral nerve has been previously reported, so some authors prefer to use the term 'sensory ataxic neuropathies'.[6] At onset 37% of our patients had asymmetric symptoms and this can be confused with mononeuritis multiplex.[3]

Despite an extensive study, in 48% of our patients we found no likely cause, similar to previous studies.[1,25] Interestingly, in 18 of these 24 otherwise idiopathic patients we found various associated markers of autoimmunity, which supports the hypothesis that a majority of SNN might be driven by a cell mediated immune response.[7,8] Antifibroblast growth factor receptor 3 antibodies have been found in some patients, especially with trigeminal ganglia involvement,[26] but their pathogenic role is still uncertain. We did not test these antibodies in our patients because serum was not saved in our retrospective study. We only found one genetic case (excluding clinically defined CANVAS), but genetic SNN might be underrepresented because we included only patients seen in a peripheral nerve clinic. Statin intake might be associated with a mild form of predominately

small fibre SNN,[27] however, we do not think this had a causative effect in any of the seven patients who were on statin-therapy, given the severity and the prominent large fibre involvement.

MRI T2 hyperintensity of the dorsal column, resulting from the degeneration of central afferent projections of the DRG,[28] has been proposed as strongly supportive for SNN and makes the diagnosis 'Probable' according to the Camdessanché criteria.[10] We found this MRI abnormality in 17%, lower than in previous reports[25,28] but more than the 4% reported by Camdessanché et al.[10] Our relatively small proportion with MRI abnormality might be explained if MRI was performed too early in the disease course. A patient with subacute SNN related to HIV had normal MRI at onset but posterior-column hyperintensity at 6 month follow up.[29] MRI in chronic SNN may also show spinal cord atrophy.[28] One of our patients showed dorsal root enhancement, also reported in anti-Hu paraneoplastic SNN[30] and another case had dorsal root enhancement followed by Wallerian degeneration and hyperintensity in the dorsal column.[31]

Raised CSF protein has been reported in SNN[10,25] and we found it in 31% of cases. We found unmatched oligoclonal bands in one patient with anti-Hu paraneoplastic syndrome.

All nerve biopsies performed showed severe axonal loss, and 26% revealed mild inflammatory response, matching previous reports.[6] This changes are nonspecific therefore nerve biopsy is not useful in the diagnosis of SNN[1] except to exclude alternative causes. Skin biopsy (which we did not perform) has been proposed as helpful in SNN, by showing non-length dependence of intraepidermal nerve fibre density helping to differentiate SNN from axonopathies.[32]

In our study, 30% showed motor nerve involvement on neurophysiological studies, as reported previously.[10,33] Severe impairment of radial SAP was reported to be more discriminative for SNN and we found it in 76% of cases. A rapid neurophysiological screening for SNN has been proposed, as a left-right SNAP asymmetry of greater than 50% in at least two pairs of nerves.[34]

The treatment depends on the aetiology, but there are no randomised trials. In paraneoplastic cases early treatment of the underlying tumour seems to be associated with a better outcome.[1] In toxic or chemotherapy-induced SNN there is no specific treatment but we report some patients with stabilisation or even improvement after stopping the toxin. Immunotherapy has been tried in paraneoplastic, autoimmune and idiopathic cases, often with disappointing results. Some improvements have been reported in Sjogren's with cyclophosphamide, mycophenolate and intravenous immunoglobulin (IVIg)[35] and in idiopathic or immune-mediated cases with steroids, IVIg or plasma exchange.[36,37] We also report some positive responses with cyclophosphamide, azathioprine, steroids, IVIg or plasma exchange but in most patients the outcome after treatment was still poor. Some authors proposed that earlier treatment could be associated with better response. In our study patients who received immune therapy during the first year since symptom onset tended to have better response to treatment, but this was not statistically significant and did not necessarily correlate with better final outcome. SNN related to gluten sensitivity can respond to gluten free diet[38] as we report in one patient who stabilised. This retrospective study with median follow-up of only 2 years did not allow us to assess how long the response to treatment was maintained.

Overall the outcome was not good, with 67% having mRS ≥3 and 46% mRS ≥4 at final follow up, meaning that SNN is a very disabling condition. Generalised areflexia, motor involvement, pseudoathetosis, high proteins in CSF and paraneoplastic aetiology were markers of very bad prognosis (mRs ≥4). Conversely, regeneration on nerve biopsy was associated with better outcome (mRs ≤2), perhaps suggesting axonopathy rather than SNN.

To our knowledge this is the largest published series of patients with SNN with assessment of response to treatment and outcome. Although about half of our patients remained idiopathic, in most of those there was some evidence of inflammation or immune disturbance. The evidence is still very weak as to whether delay in treatment might mean worse response to immune therapy, so the time window for treatment remains unclear. SNN is a very disabling condition, especially patients with generalised areflexia and pseudoathetosis. Some patients had a positive response to immunotherapy, but rarely enough to make a big difference to disability and some patients remained confined to wheelchair. Larger prospective studies are necessary for better understanding of this heterogeneous disease, allowing an early diagnosis and guiding future randomised treatment trials.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ORCID

Agustin Sancho Saldaña https://orcid.org/0000-0003-4008-9436

REFERENCES

1. Sghirlanzoni A, Pareyson D, Lauria G. Sensory neuron diseases. *Lancet Neurol*. 2005;4(6):349-361.
2. Gwathmey KG. Sensory neuronopathies. *Muscle Nerve*. 2016;53(1):8-19.
3. Kuntzer T, Steck AJ. Sensory neuronopathies or ganglionopathies 2015;273–89.
4. Sheikh SI, Amato AA. The dorsal root ganglion under attack: the acquired sensory ganglionopathies. *Pract Neurol*. 2010;10(6):326-334.
5. Gwathmey KG. Sensory polyneuropathies. *Contin Lifelong Learn Neurol*. 2017;23:1411-1436.
6. Dalakas MC. Chronic idiopathic ataxic neuropathy. *Ann Neurol*. 1986;19(6):545-554.
7. Hainfellner JA, Kristoferitsch W, Lassmann H, et al. T cell-mediated ganglionitis associated with acute sensory neuronopathy. *Ann Neurol*. 1996;39(4):543-547.
8. Colli BO, Carlotti CG, Assirati JA, et al. Dorsal root ganglionectomy for the diagnosis of sensory neuropathies. Surgical technique and results. *Surg Neurol*. 2008;69(3):266-273.
9. Jankowicz E, Drozdowski W. Sensory neuronopathy. *Neurol Neurochir Pol*. 1999;33(3):621-632.
10. Camdessanché JP, Jousserand G, Ferraud K, et al. The pattern and diagnostic criteria of sensory neuronopathy: a case-control study. *Brain*. 2009;132(7):1723-1733.
11. Antoine JC, Robert-Varvat F, Maisonobe T, et al. Testing the validity of a set of diagnostic criteria for sensory neuronopathies: a francophone collaborative study. *J Neurol*. 2014;261(11):2093-2100.

12. Gorson KC, Herrmann DN, Thiagarajan R, et al. Non-length dependent small fibre neuropathy/ganglionopathy. *J Neurol Neurosurg Psychiatry*. 2008;79(2):163-169.
13. Breiner A, Moher D, Brooks J, et al. Adult CSF total protein upper reference limits should be age-partitioned and significantly higher than 0.45 g/L: a systematic review. *J Neurol*. 2019;266(3):616-624. https://doi.org/10.1007/s00415-018-09174-z.
14. Graus F, Delattre JY, Antoine JC, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes. *J Neurol Neurosurg Psychiatry*. 2004;75(8):1135-1140.
15. Haberberger RV, Barry C, Dominguez N, Matusica D. Human dorsal root ganglia. *Front Cell Neurosci*. 2019;13:1-17.
16. Dalmau J, Furneaux HM, Rosenblum MK, Graus F, Posner JB. Detection of the anti–Hu antibody in specific regions of the nervous system and tumor from patients with paraneoplastic encephalomyelitis/sensory neuronopathy. *Neurology*. 1991;41(11):1757-1764.
17. Graus F, Campo E, Cruz-Sanchez F, Ribalta T, Palacin A. Expression of lymphocyte, macrophage and class I and II major histocompatibility complex antigens in normal human dorsal root ganglia. *J Neurol Sci*. 1990;98(203):203-211.
18. Emery EC, Ernfors P, Emery EC, Ernfors P. Dorsal root ganglion neuron types and their functional specialization. In: Wood JN, ed. *The Oxford Handbook of the Neurobiology of Pain*. London: Oxford University Press; 2018:1-32.
19. Lawson SN. The postnatal development of large light and small dark neurons in mouse dorsal root ganglia: a statistical analysis of cell numbers and size. *J Neurocytol*. 1979;8(3):275-294.
20. Sharp. Pseudoathetosis: loss of proprioception. 1994
21. Szmulewicz DJ, Roberts L, McLean CA, MacDougall HG, Michael Halmagyi G, Storey E. Proposed diagnostic criteria for cerebellar ataxia with neuropathy and vestibular areflexia syndrome (CANVAS). *Neurol Clin Pract*. 2016;6(1):61-68.
22. Camdessanché JP, Antoine JC, Honnorat J, et al. Paraneoplastic peripheral neuropathy associated with anti-Hu antibodies. A clinical and electrophysiological study of 20 patients. *Brain*. 2002;125(1):166-175.
23. Rothwell JC, Traub MM, Day BL, Obeso JA, Thomas PK, Marsden CD. Manual motor performance in a deafferented man. *Brain*. 1982;105(3):515-542.
24. Martinez ARM, Martins MP, Martins CR, et al. Sensory ataxia rating scale: development and validation of a functional scale for patients with sensory neuronopathies. *J Peripher Nerv Syst*. 2019;24(3):242-246.
25. Damasceno A, França MC, Nucci A. Chronic acquired sensory neuron diseases. *Eur J Neurol*. 2008;15(12):1400-1405.
26. Antoine JC, Boutahar N, Lassablière F, et al. Antifibroblast growth factor receptor 3 antibodies identify a subgroup of patients with sensory neuropathy. *J Neurol Neurosurg Psychiatry*. 2015;86(12):1347-1355.
27. Novak P, Pimentel DA, Sundar B, Moonis M, Qin L, Novak V. Association of statins with sensory and autonomic ganglionopathy. *Front Aging Neurosci*. 2015;7:3-8.
28. França MC, D'Abreu A, Zanardi VA, et al. MRI shows dorsal lesions and spinal cord atrophy in chronic sensory neuronopathies. *J Neuroimaging*. 2008;18(2):168-172.
29. Numakura C, Lin C, Oka N, Akiguchi I, Hayasaka K. Hemizygous mutation of the peripheral myelin protein 22 gene associated with Charcot-Marie-Tooth disease type 1. *Ann Neurol*. 2000;47(1):101-103.
30. Shibui A, Kobayashi J, Kuroda H, Aoki M. Dorsal root enhancement in paraneoplastic sensory ataxic neuropathy with anti-Hu antibody. *Neurol Clin Neurosci*. 2016;4(1):22-24.
31. Endo K, Suzuki N, Misu T, Aoki M, Itoyama Y. Dorsal-roots enhancement and Wallerian degeneration of dorsal cord in the patient of acute sensory ataxic neuropathy. *J Neurol*. 2009;256(10):1765-1766.
32. Lauria G, Sghirlanzoni A, Lombardi R, Pareyson D. Epidermal nerve fiber density in sensory ganglionopathies: clinical and neurophysiologic correlations. *Muscle Nerve*. 2001;24(8):1034-1039.
33. Lauria G, Pareyson D, Sghirlanzoni A. Neurophysiological diagnosis of acquired sensory ganglionopathies. *Eur Neurol*. 2003;50(3):146-152.
34. Zis P, Hadjivassiliou M, Sarrigiannis PG, Barker ASJE, Rao DG. Rapid neurophysiological screening for sensory ganglionopathy: a novel approach. *Brain Behav*. 2017;7(12):3-7.
35. Pereira PR, Viala K, Maisonobe T, et al. Sjögren sensory neuronopathy (Sjögren Ganglionopathy) long-term outcome and treatment response in a series of 13 cases. *Medicine (United States)*. 2016;95(19):1-6.
36. Zuberbuhler P, Young P, León Cejas LV, et al. Sensory neuronopathy. Its recognition and early treatment. *Medicina (B Aires)*. 2015;75(5):297-302.
37. Hussain A, Scelsa SN. Sensory neuronopathy with Ro antibodies: response to combination immunosuppression. *J Clin Neuromuscul Dis*. 2010;11(3):120-123.
38. Hadjivassiliou M, Sanders DS, Gru RA. Sensory ganglionopathy due to gluten sensitivity-Hadjivassiliou et al. *Neurology*. 2010;75(11):1003.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Sancho Saldaña A, Mahdi-Rogers M, Hadden RD. Sensory neuronopathies: A case series and literature review. *J Peripher Nerv Syst*. 2021;26:66–74. https://doi.org/10.1111/jns.12433