

REVIEW

Pain as a First Manifestation of Paraneoplastic Neuropathies: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Paraneoplastic neurological syndromes (PNS) consist of a heterogeneous group of neurological disorders triggered by cancer. The aim of this systematic review is to estimate the reported prevalence of pain in patients with paraneoplastic peripheral neuropathy (PPN).

Methods: A systematic computer-based literature search was conducted on PubMed database.

Results: Our search strategy resulted in the identification of 126 articles. After the eligibility

assessment, 45 papers met the inclusion criteria. Full clinical and neurophysiological data were further extracted and involved 92 patients with PPN (54.5% males, mean age 60.0 ± 12.2 years). The commonest first manifestation of PPN is sensory loss (67.4%), followed by pain (41.3%), weakness (22.8%), and sensory ataxia (20.7%). In 13.0% of the cases, pain was the sole first manifestation of the PPN. During the course of the PPN, 57.6% of the patients may experience pain secondary to the neuropathy.

Conclusions: Pain is very prevalent within PPN. Pain specialists should be aware of this. Detailed history-taking, full clinical examination, and requesting nerve conduction studies might lead to an earlier diagnosis of an underlying malignancy.

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INTRODUCTION

Paraneoplastic neurological syndromes (PNS) consist of a heterogeneous group of neurological disorders triggered by cancer. These syndromes are caused by mechanisms other than metastases, metabolic or nutritional deficits, infections, coagulopathy, or side effects of cancer treatment such as chemotherapy. The discovery that many PNS are associated with antibodies against neural antigens expressed by

the tumor (antineural antibodies) has suggested that PNS are immune-mediated [1].

The recommended diagnostic criteria for PNS [2] suggest that the cancer has to develop within 5 years of the diagnosis of the neurological disorder. This time period has been based on reports showing that in the majority of cases the interval between the PNS and the diagnosis of cancer is less than 5 years.

Paraneoplastic peripheral neuropathy (PPN) is one of the commonest PNS reported. The aim of this paper is to systematically review the presenting manifestations of patients with PPN and establish the reported prevalence of pain. This article follows on from the editorial introduction “Painful Peripheral Neuropathy and Cancer” (doi:10.1007/s40122-017-0077-2).

METHODS

Literature Search Strategy

A systematic computer-based literature search was conducted on April 6th, 2017 on PubMed database. For the search, we used three Medical Subject Headings (MeSH) terms. Term A was “neuronopathy” or “ganglionopathy” or “neuropathy”, term B was “paraneoplastic” and term C was “first manifestation” or “first symptom” or “initial symptom” or “first manifestations” or “first symptoms” or “initial symptoms” or “presenting symptom” or “presenting symptoms” or “pain” or “painful”. Limitations included language to be English and full text to be available. We also used the reference lists of the papers in order to find papers not found through the search strategy.

Inclusion and Exclusion Criteria

To be included in the review, the articles had to meet the following criteria:

- (1) To involve single cases or cases series with PPN.
- (2) To study human adult subjects.

The following exclusion criteria were applied:

- (1) Book chapters, reviews, letters to the editor and editorials that did not provide new data.

- (2) Papers referring only to autonomic neuropathy.
- (3) Papers referring only to cranial neuropathies.
- (4) Papers referring only to small fiber neuropathies.
- (5) Papers referring to POEMS (Polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes) syndrome.
- (6) Papers referring to motor neuron disease.
- (7) Papers providing incomplete clinical or neurophysiological data about the single cases/case series.

Data Extraction

Data were extracted from each study in a structured coding scene using Microsoft Excel and included information on the article identification, year of publication, evaluation period, total number of subjects, gender, age, first manifestation of the PPN, presence of pain secondary to the neuropathy, neurophysiological type of neuropathy, course of symptoms, type of cancer, and presence of anti-neuronal antibodies.

We used the International Association for the Study of Pain (IASP) definitions to classify pain as neuropathic or not.

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

Statistical Analyses

A database was developed using the IBM SPSS Statistics (version 23.0 for Mac). Frequencies and descriptive statistics were examined for each variable. The primary outcomes of interest were the proportion of patients who experienced pain as a first manifestation of the PPN and the proportion of patients who experienced pain during their PNS. Further comparisons between groups were made using Student’s *t* test for continuous data and Chi-square test for categorical data. A value of $P < 0.05$ was considered to be statistically significant.

RESULTS

Search Results

This search strategy resulted in the identification of 126 articles. After the eligibility assessment, 81 articles were excluded. In total, 45 papers met the inclusion criteria and were used for this review [3–47]. These studies were published between 1984 and 2017. Figure 1 illustrates the study selection process.

Full clinical and neurophysiological data were further extracted from 42 papers and involved 92 patients with PPN (54.5% males). The age of the patients ranged from 18 to 81 years (mean 60.0 ± 12.2 years). The demographic and clinical characteristics of these patients are summarized in Table 1.

Epidemiological Characteristics of PPN

Although PPN is said to be the commonest PNS (34.9%), followed by encephalomyelitis (23.8%) and cerebellar degeneration (20.6%) [45], there is sparse epidemiological data on the prevalence of neurophysiologically confirmed PPN. The reasons for this are two-fold. The available studies to date are either in cohorts of patients with known malignancy and neuropathic symptoms or in patients who are seropositive for well-characterized paraneoplastic antibodies. A correct prevalence study of PPN should include a large cohort of patients with newly diagnosed malignancy all of whom should be evaluated for the presence of PN with nerve conduction studies, even in the absence of neuropathic symptoms and paraneoplastic antibodies.

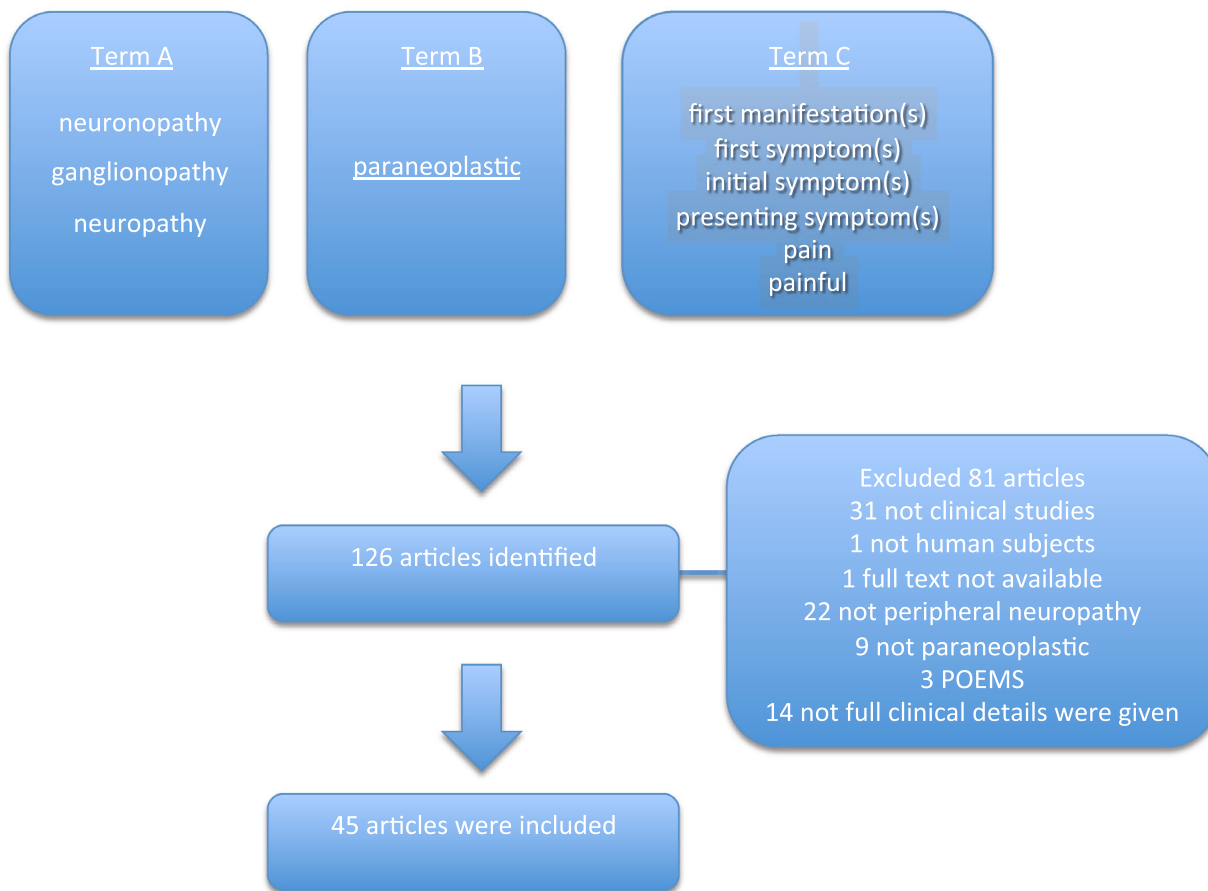


Fig. 1 PRISMA chart

Table 1 Descriptive of studies included in the meta-analysis

Parameter	Value
Number of papers ^a	42
Type of papers	
Case report (%)	29 (75.0)
Case series (%)	13 (25.0)
Total number of patients	92
Male:female	3:2
Mean age, in years (SD)	60.0 (12.2)
Presenting manifestations (%)	
Ataxia	19 (20.7)
Sensory deficit	62 (67.4)
Pain	38 (41.3)
Weakness	21 (22.8)
Pain at any point (%)	53 (57.6)
Type of pain (%)	
Neuropathic	51 (96.2)
Nociceptive	2 (3.8)
Type of neuropathy (%)	
Axonal	80 (87.0)
Symmetrical sensorimotor	21 (22.8)
Symmetrical sensory	21 (22.8)
Sensory ganglionopathy	25 (27.2)
Mononeuritis multiplex	6 (6.5)
Pure motor	7 (7.6)
Demyelinating	12 (13.0)
Temporal evolution of neuropathy (%)	
Acute	12 (13.0)
Sub-acute	59 (64.1)
Progressive/chronic	21 (22.8)
Type of malignancy (%)	
Lung	42 (45.7)
Mediastinal	4 (4.3)
Hematological	15 (16.3)

Table 1 continued

Parameter	Value
Gastro-intestinal	11 (12.0)
Gynecological	8 (8.7)
Other	6 (6.5)
Unknown primary	6 (6.5)
Anti-Hu antibodies ^b (%)	47 (61.8)

SD standard deviation

^a Three more papers provided useful information on epidemiology and were used in the review, but they did not provide full clinical data on individual cases

^b Tested in 76 patients

Lucchinetti et al. [47] estimated that out of 162 patients seropositive for anti-Hu antibodies (anti-neuronal antibodies usually associated to small-cell lung carcinoma), 72.8% presented with neuropathic symptoms. Most commonly, the patients presented with pure sensory (40.1%), followed by mixed sensory and motor (30.2%) and pure motor symptoms (2.4%) [47]. However, no neurophysiological data were provided in this study.

In another series of 150 patients with a biopsy confirmed SCLC, Elrington et al. [6] estimated that the prevalence of sensory symptoms was 16% and the prevalence of motor symptoms 44%. However, a definite neuropathy was confirmed with nerve conduction studies only in one patient (0.7% of the total study population).

Graus et al. [46] presented a series of 200 patients, seropositive for anti-Hu antibodies, and estimated that 54% were present with predominantly sensory neuropathy and 4.5% with sensorimotor neuropathy. However, no information was given about whether nerve conduction studies were done in all patients, and what type of neuropathy these patients presented with.

Clinical Manifestations of PPN

The commonest early manifestation of PPN is sensory loss (67.4%), followed by pain (41.3%), weakness (22.8%), and sensory ataxia (20.7%).

In 39.1% of the cases, the presenting complaints included more than one symptom. However, in 13.0% of the cases, pain was the sole first manifestation of the PPN. During the course of the PPN, 57.6% of the patients reported pain secondary to the neuropathy. In the majority of these patients (96.2%), the pain was directly related to the neuropathy (considered as neuropathic) as described in the papers included in this review; however no validated tools were used to systematically assess and record other neuropathic symptoms accompanying pain. A minority of patients reported pain indirectly related to the neuropathy (not neuropathic), secondary to painful muscle cramps.

Temporal Evolution of PPN and Pain

Most reports classified PPN as acute, sub-acute or chronic/progressive. Acute were those neuropathies that evolved within 1 month, sub-acute were those that evolved between 1 and 6 months, and chronic the neuropathies that slowly kept progressing beyond 6 months. Based on these reports, we estimated that PPN are sub-acute in the majority of cases (64.1%), followed by chronic (22.8%) and acute (13.0%).

Neurophysiological Types of PPN and Pain

Large fiber neuropathy can be axonal or demyelinating. In axonal neuropathy, axons are affected usually in proportion to their length (length dependent). In demyelinating neuropathy, the myelin sheath around axons is affected, and as a result, the ability of the axons to speedily conduct electrical impulses is impaired. The latter leads to slow or no conduction (conduction block). Sensory neuropathy, or ganglionopathy, is another large fiber peripheral neuropathy, in which the cell bodies of the sensory neurons located in the dorsal root ganglia are affected. Finally, in pure motor neuropathy, there is involvement of only the lower motor neurons [48].

Demyelinating neuropathies were reported in 13% of PPN cases. Among the axonal PPN (87%), the most common neurophysiological type was asymmetrical sensory ganglionopathy

(27.2%), followed by symmetrical sensorimotor neuropathy (23.9%), symmetrical sensory neuropathy (21.7%), pure motor neuropathy (7.6%), and mononeuritis multiplex (6.5%). Figure 2 illustrates how common is pain based on the neurophysiological type of the PPN.

Though rare, the most painful type of PPN is mononeuritis multiplex. Mononeuritis multiplex is known to occur in many illnesses including certain types of systemic vasculitis [49]. Indeed, in the majority of patients with paraneoplastic mononeuritis multiplex a nerve biopsy was performed, showing evidence for vasculitis [36, 39].

Although pure motor neuropathy is the least common, it can still be painful. The major difference in the pain reported in such cases is that it is muscular in nature, most commonly because of cramps [40].

Paraneoplastic Antibodies and Painful PPN

Out of 76 patients with painful PPN tested for anti-Hu antibodies, 47 were positive (61.8%). Other antibodies that have been associated with PPN are anti-amphiphysin and anti-CV2 antibodies. Interestingly enough, patients with anti-Hu antibodies were more likely to present with pain as a first manifestation compared to patients without anti-Hu antibodies (53.2 vs. 24.1%, $p = 0.013$). Also, patients with anti-Hu antibodies were more likely to present with pain secondary to the PPN at any point compared to patients without anti-Hu antibodies (74.5 vs. 41.4%, $p = 0.004$).

Cancer Types and Painful PPN

Lung cancer was the commonest cause of PPN (45.7%), followed by hematological malignancies (16.3%) and gastro-intestinal tract malignancies (12.0%). The majority of patients seropositive for anti-Hu had lung cancer (66.0%). Detailed data regarding type of malignancy are shown in Table 1. Cancer type was not related significantly to pain either as a first manifestation or during the course of the PPN ($p > 0.05$).

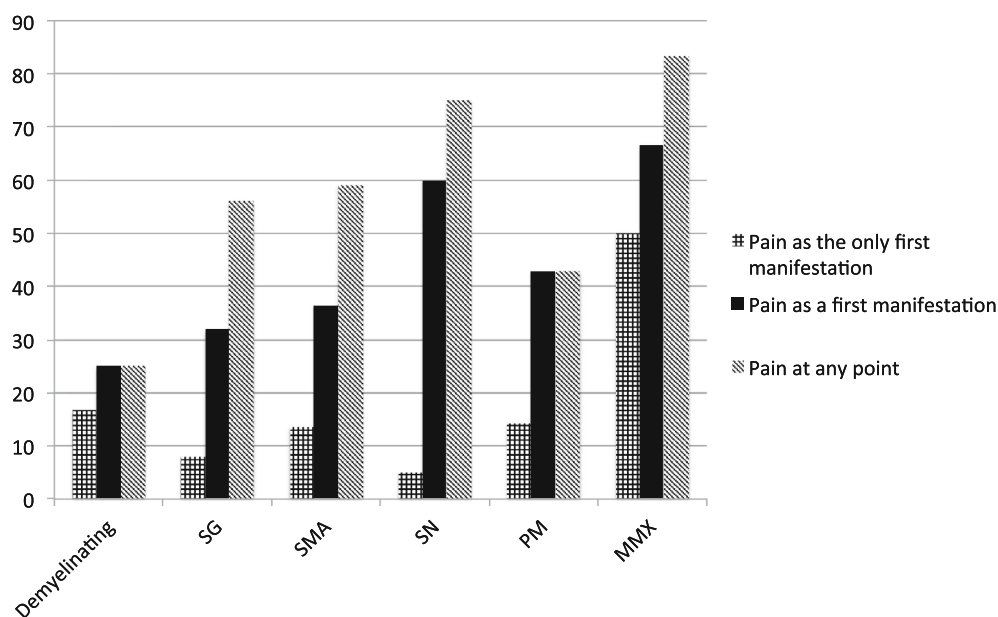


Fig. 2 Pain as a symptom among the different neurophysiological types of paraneoplastic peripheral neuropathies given in percentages. *SG* sensory

ganglionopathy, *SMA* sensorimotor axonal neuropathy, *SN* symmetrical sensory neuropathy, *PM* pure motor neuropathy, *MMX* mononeuritis multiplex

PPN and Cancer Relapse

PNS can be the first manifestation of cancer relapse [8, 17, 20] and they often precede the clinical or radiological diagnosis of a local relapse or distant metastases. Patients with a history of cancer presenting with peripheral neuropathic pain, not otherwise explained, can be diagnosed with PNS when circulating paraneoplastic antibodies are detected or a PET scan is positive.

Management

Management of pain as a result of paraneoplastic neuropathy does not differ from the published guidelines on the management of neuropathic pain [50]. However, it is commonly reported that treatment for the underlying malignancy (including tumor resection and/or chemotherapy) can improve the symptoms [3, 11, 28, 30, 37].

CONCLUSIONS

This systematic review and meta-analysis indicates the following key points:

- (1) Pure sensory neuropathy (sensory ganglionopathies and symmetrical sensory neuropathies) is the commonest form of PPN reported. A full neurophysiological assessment is therefore advisable in all suspected cases. Such a finding may prompt searching for an underlying malignancy.
- (2) The commonest first manifestation of PPN is sensory loss (67.4%), followed by pain (41.3%), weakness (22.8%), and sensory ataxia (20.7%).
- (3) Pain is prevalent in PPN, as almost three out of five patients with PPN will experience peripheral neuropathic pain at some point in the course of the PNS. The majority of the patients will experience neuropathic pain, but patients with pure motor neuropathies also experience pain secondary to cramps.
- (4) One out of seven patients with PPN will experience pain as the sole manifestation. Therefore, pain specialists should be aware that they may be the first to encounter patients whose pain may be a paraneoplastic phenomenon. Therefore, detailed

history taking, full clinical examination, and neurophysiological assessment—especially of sub-acute onset and of unknown etiology—may lead to an earlier diagnosis of an underlying malignancy.

- (5) Testing for paraneoplastic antibodies (i.e., anti-Hu and anti-CV2), especially in sensory neuropathies that evolve sub-acutely, might also be helpful in earlier diagnosis of a PPN.
- (6) PNS can occur as part of cancer relapse and pain can be the first manifestation in such cases. Therefore, patients with a past history of malignancy who present with neuropathic symptoms, including pain and have evidence of a PN on neurophysiology should be investigated further for a possible relapse. A PET scan might be useful in the earlier diagnosis of PNS [27].
- (7) Among the papers included in this review, different terms have been used to describe the presenting symptoms. The use of validated tools [51] for assessing the presence of pain and the quality of the related characteristics might be useful for future prospective studies.

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Disclosures. Panagiotis Zis, Antonella Paladini, Alba Piroli, Patrick C. McHugh, Giustino Varrassi and Marios Hadjivassiliou have nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

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