Postherpetic neuralgia, diabetic neuropathy, and trigeminal neuralgia – Chronic peripheral neuropathic pain in 58,480 rural Italian primary care patients

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Abstract

Introduction: Chronic peripheral neuropathic pain (CPNP) is a condition due to peripheral nervous system diseases or injury, but its prevalence is unknown in Italian primary care. Aim: The aim of this study is to assess the prevalence of CPNP in a rural primary care area in Northern Italy. Materials and Methods: A multicenter audit study was carried out in a rural area in Northern Italy with 113 participating general practitioners (GPs) seeing 58,480 patients >18 years during 3 months. Patients who for any reason attended GPs’ surgeries and had symptoms suggestive of neuropathic pain (NP) were given the NP diagnostic questionnaire “Douleur Neuropathique en 4 Questions” (DN4) and recorded their pain level on a visual analog scale (VAS). Results: Chronic NP was established by a DN4 score of ≥4 and a VAS pain score of ≥40 mm for >6 months together with a clinical diagnosis in 448 (254 women and 194 men) out of 58,480 patients giving a prevalence of 0.77%. 179 patients (0.31%) had diabetes neuropathy, 142 (0.24%) had postherpetic pain, 41 (0.07%) had trigeminal neuralgia, 27 (0.05%) had NP postinjury, 27 (0.05%) had NP caused by nerve entrapments, 11 (0.02%) had NP triggered by systemic diseases, and 21 (0.04%) had NP of unknown etiology. Conclusions: The prevalence of CPNP in this population of primary care attenders in a rural area in Northern Italy was 0.77%. Diabetes neuropathy (0.31%) and postherpetic pain (0.24%) were the two most common subgroups of NP, followed by trigeminal neuralgia (0.07%).

Keywords: Chronic peripheral neuropathic pain, diabetes neuropathy, general practitioners, herpetic pain, neuropathic pain diagnostic questionnaire, prevalence, visual analog scale

Introduction

Neuropathic pain (NP) is a pain caused by damage or disease affecting the somatosensory system.¹ Disorders of the brain or spinal cord can lead to “central pain,” such as that encountered in multiple sclerosis, after a stroke, and in spondylotic and posttraumatic myelopathy. Peripheral nervous system disorders include diseases of the spinal nerve roots, dorsal root ganglia, and peripheral nerves. Classical examples include diabetic polyneuropathies, postherpetic neuralgia, and trigeminal neuralgia.² NP is associated with depression, anxiety disorders, and impairment of sleep quality. All these translate into a loss of quality of life also affecting the family of patients and their social and working environment.³⁴

Research on chronic peripheral NP (CPNP) is still lacking and progress in this field is developing slowly.⁵ Most NP patients are still unrecognized and inappropriately treated.⁶⁷ NP is estimated to afflict as much as 7%–8% of the general population.

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in Europe.[31] An American study showed that 1/3 of patients affected by malignancies suffered from NP or a mix of NP and nociceptive pain.[12]

The Canadian Pain Society developed treatment guidelines of CPNP and estimated a 2%–3% prevalence.[13] In Italy, about 200,000 people are affected by herpes zoster annually and many develop postherpetic neuralgia.[14] NP is widely prevalent and associated with so many diverse diseases that primary care physicians meet many NP patients[15] and hold a key diagnostic position because they guide the early management of pain and have a pivotal role in triaging patients for specific treatment approaches.[16]

Rural residency is associated with higher prevalence of chronic pain and other psychiatric and medical comorbidities, especially depression.[17,18] Rural residents with chronic pain report higher pain frequency and intensity, as well as more pain-related disability and depression than people with pain living in urban areas.[19,20]

Since there are no comprehensive studies on CPNP in Italian primary care, the aim of this study was to investigate its prevalence in a primary care setting in a rural area in Northern Italy.

Materials and Methods

The setting of the study was general practices in five adjoining provinces in a rural area in Northern Italy where all 243 general practitioners (GPs) were contacted by phone, invited to take part in a continuous medical education (CME) NP training course, and recruit patients to the present study. Eventually, 113 out of 243 GPs - participation rate 46% - participated in the CME NP course and took part in this study. The participating 113 GPs cared for a population of 116,752 listed patients. A consecutive sample of all of GP patients ≥18 years of age attending general practice services for any reason, over a period of 3 months, who also complained of alleged symptoms of NP, was first assessed clinically and included in the study if they met the inclusion criteria below.

Exclusion criteria

Patients with nociceptive pain and central NP, serious psychiatric disorders, and any other clinically relevant disease preventing neuropathy assessment or accurate understanding of the questionnaires were excluded from the study.

Measures

A full history of the onset and the nature of the patient’s pain was first assessed. Next, a detailed neurologic and musculoskeletal clinical examination was performed, using simple tools for assessment of sensory function guided by the information obtained from the patient history and pain drawings.[21] The presence of chronic NP in the same areas and with the same distal distribution of neuropathic sensory symptoms was considered indicative for a diagnosis of chronic NP.[6]

The diagnostic tool “Douleur Neuropathique en 4 Questions” (DN4)[22] was used to determine a NP diagnosis [Figure 1]. DN4 consists of 10 items: 7 items concern the quality of pain, and are obtained by interviewing the patients, whereas 3 items are based on clinical examination and analyze the presence or absence of touch or pinprick hypoesthesia and tactile allodynia. A score of 1 is given to each positive item and a score of 0 to each negative item. Scores ≥4 out of 10 are considered indicative of NP. DN4 has been translated into 15 languages and has been used in epidemiological studies in the general population and in patients with diabetes.[23] In Italy DN4 has been validated to identify painful diabetic polyneuropathy.[24] Padua et al. showed that DN4 was more accurate in the diagnosis of NP than ID-Pain - a 6-item questionnaire.[25]

The intensity of pain was evaluated on a visual analog scale (VAS) of 100 mm.[26] For the VAS, we asked the patients to mark the level of their pain on a 100-mm line marked at one end as “no pain” and at the other as “worst pain imaginable.”

Patients were defined as being affected by CPNP if they had a clinical diagnosis of peripheral NP together with a DN4 score of ≥4 and a VAS score of ≥40 mm with pain duration of ≥6 month.

Figure 1: “Douleur Neuropathique 4 question” questionnaire translated into Italian and English. Every yes answer is given 1 point. The cutoff value of the questionnaire is 4 points or more.
Other variables registered were weight, height, systolic and diastolic blood pressure, smoking status, alcohol consumption, and comorbidities such as diabetes, sleep disorder, depression, and anxiety.

Data analysis

The prevalence of CPNP was calculated as the ratio between patients enrolled and the total number of patients who attended the GPs offices in 3 months. Patients attending more than one time in the observational period were counted only once.

Data were evaluated by descriptive statistics using a P = 0.05 as cutoff and the Mann–Whitney/Wilcoxon test for data not normally distributed. Statistical analysis was performed using Epi Info® 2011 version 3.5.3 (CDC, Atlanta, USA).

Data protection, confidentiality, and ethical issues

Patients’ identities were protected and no individual subjects could be identifiable from the data. A patient information sheet with simple information about the research was given to all the patients and GPs involved and patients who agreed to participate signed an informed consent form. Formal research ethics committee approval was not required as this was neither an interventional nor an observational study on pharmacological treatment. In Italy, a notification is only required by the ethics committees of participating centers for this type of study, and the approval begins 60 days following the date of notification using an opt-out silence consent procedure.

Results

One hundred and thirteen GPs with 116,752 patients listed aged ≥18 years took part in the study. The number of patients who consulted GPs’ surgeries in 3 months was 58,480 (mean age 48 years, 63% women and 37% men) and the number of patients with suggestive symptoms of NP were 480 (0.82%, mean age 69 years, 273 [57%] women and 207 [43%] men). The basal features of the eligible 480 patients are reported in Table 1. Of them, 32 (19 women and 13 men) did not reach inclusion criteria, and eventually, 448 patients (mean age 69 years, 254 [57%] women and 194 [43%] men) were diagnosed with CPNP giving a prevalence of 0.77%. Diabetes (n = 179), herpes zoster (n = 142), trigeminal neuralgia (n = 41), trauma (n = 27), nerve entrapment (n = 27), systemic diseases (n = 11), and unknown causes (n = 21) were the etiological determinants of CPNP in our study. The median DN4 score was 6 (range: 4–10) in all NP patients, and the median VAS pain score was 70 mm (range: 40–100), showing uniformity in the intensity of pain as no record fell below 60 mm. Frequent intercurrent morbidities were poor sleeping quality (23%), anxiety (39%), depression (23%), and insomnia (31%).

Results of assessments of the two biggest groups of patients - diabetes neuropathy and postherpetic NP - are compared in Table 2. Patients with diabetes neuropathy were slightly older, but their DN4 scores and VAS scores did not differ from patients with postherpetic NP.

| Table 1: Italian chronic peripheral neuropathic pain prevalence study of 113 general practitioners seeing 58,480 patients >18 years during 3 months |
|-----------------------------------------------|-----------------|-----------------|
| Number of patients                          | Eligible patients | Chronic peripheral NP patients |
| Men (%)                                      | 207 (43)         | 194 (43)         |
| Women (%)                                    | 273 (57)         | 254 (57)         |
| Mean age, years                             | 69±13            | 69±12            |
| Median DN4 score                            | 6 (4-10)         | 6 (4-10)         |
| Median VAS score, mm                        | 70 (40-100)      | 70 (40-100)      |
| Mean systolic blood pressure, mmHg          | 129±2            | 129±2            |
| Mean diastolic blood pressure, mmHg         | 87±2             | 87±2             |
| Mean BMI, kg/m²                              | 26.5             | 26.5             |
| Diabetes (%)                                 | 192 (40)         | 179 (40)         |
| History of herpes zoster (%)                 | 144 (30)         | 142 (32)         |
| Sleep disturbance (%)                        | 112 (23)         | 105 (23)         |
| Anxiety (%)                                  | 190 (39)         | 180 (40)         |
| Depression (%)                               | 112 (23)         | 102 (23)         |
| Insomnia (%)                                 | 147 (31)         | 138 (31)         |
| Daily smoker (%)                             | 65 (14)          | 61 (14)          |
| Daily alcohol consumption (%)                | 105 (22)         | 96 (21)          |

| Table 2: Basal features of 448 eligible patients with chronic peripheral neuropathic pain. Patients with diabetes and postherpetic neuropathic pain are compared with respect to comorbidities smoking, alcohol, and demographic data |
|-----------------------------------------------|-----------------|------------------|
| Number of patients                           | All chronic peripheral NP patients | Diabetes NP Postherpetic NP |
| Number of patients (%)                       | 448             | 179 (39)         | 142 (30)         |
| Men (%)                                      | 194 (43)        | 88 (49)          | 54 (40)          |
| Women (%)                                    | 254 (57)        | 90 (51)          | 82 (60)          |
| Mean age, years                              | 68±13           | 71±19.9*         | 66±15*           |
| Median DN4 score                             | 6 (4-10)        | 6 (4-10)         | 6 (4-10)         |
| Median VAS score, mm                         | 70 (40-100)     | 70 (40-100)      | 70 (40-100)      |
| Mean systolic blood pressure, mmHg           | 129±2           | 129±1.9          | 129±1.8          |
| Mean diastolic blood pressure, mmHg          | 82±1.9          | 87±1.9           | 87±1.7           |
| Mean BMI, kg/m²                               | 26±5            | 28±5             | 25±4             |
| Sleep disturbance (%)                         | 106 (23)        | 41 (23)          | 29 (21)          |
| Anxiety (%)                                   | 182 (40)        | 62 (35)          | 60 (44)          |
| Depression (%)                                | 104 (23)        | 33 (19)          | 35 (24)          |
| Insomnia (%)                                  | 141 (31)        | 49 (28)          | 42 (31)          |
| Daily smoker (%)                              | 61 (14)         | 49 (28)          | 42 (31)          |
| Daily alcohol consumption (%)                 | 105 (22)        | 36 (20)          | 33 (24)          |

*Mann–Whitney/Wilcoxon test; P<0.05. NP: Neuropathic pain; DN4: Douleur Neuropathique en 4 Questions; VAS: Visual analog scale; BMI: Body mass index
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Discussion

Main findings
This is the first prevalence study of CPNP in a rural primary care setting in Italy where 113 Italian GPs diagnosed CPNP in 448 out of 58,480 patients (0.77%) during 3 months using a VAS pain scale and the diagnostic DN4 questionnaire - a valuable tool in daily practice[23] - easy to use and allowing an immediate diagnosis[23,24]

Study results in relation to existing literature
NP is a common condition, with a prevalence from 1% to 6.9% in the general population to 8%–9% in elderly adults[2,11] The prevalence in our population (0.77%) was lower than in studies from the UK (1%),[10] the US (1.3%),[10] and Canada (2%–3%).[13] A population-based survey of NP characteristics in 6000 patients treated in family practices in the UK reported a prevalence of 8% for pain of predominantly neuropathic origin. Patients with NP reported more intense and long-lasting pain and more greatly impaired quality of life compared to respondents with other types of chronic pain.[9] Similarly, a large population-based study in France found that 6.9% reported chronic pain with neuropathic characteristics, with greater severity of symptoms compared with other chronic pain types.[10] The prevalence rate found in the current study was not comparable with other studies since the group of participants studied and the methods used were not similar. In addition, there is no criterion standard for diagnosing NP.

What was useful information in the study was the severity of the pain. In fact, the median VAS pain score was 70 mm (range: 40–100), showing uniformity in the intensity of pain as no record fell below 60 mm. Pain in rural areas is an extremely understudied area of research. Patients with pain living in rural areas are often underserved and poor.[3] They report more pain severity and co-occurring psychological distress with lower or limited access to healthcare services than individuals with chronic pain living in urban areas.[9] One of the most important comorbidities, which increases pain severity, is depression.[8,17] In this study, 23% of CPNP patients suffered from depression, and this may have contributed to enhance pain severity level in these subjects.

Further studies should be made to assess the role of psychological factors in these rural areas.

Strengths and limitations of the study
Frequent problems for patients in the study were poor sleeping quality, anxiety, depression, and insomnia. Anxiety and poor sleep quality lower the pain threshold, thereby increasing pain intensity,[32] yet pain interferes with sleep ability and can also induce anxiety and depression. Hence, depression may be both a cause and a consequence of CPNP.

A major hurdle in establishing a correct diagnosis in this study was the previous lack of unambiguous diagnostic criteria for distinguishing NP from nociceptive pain and Italian GPs are not yet used to making this diagnosis. Furthermore, the short period of recruitment in our study may have caused a shortage in the enrollment and exclusion criteria, aimed to exclude confounding factors, may also have limited the number of diagnoses which may have underestimated the true prevalence.

Another group that was missed was those who did not present to a GP during the 3-month observation period. NP is often chronic, and most sufferers are on long-term medication, not necessarily requiring frequent visits in primary care, and therefore may be under-detected in our study.

Implications for clinical practice, education, or research
Two major considerations emerge from the high median value of VAS (70 mm) and DN4 score (6 points) in this study. In patients with CPNP, symptoms were not always so well defined or easily identifiable, but usually at a considerable level of intensity. Better tools in the CME are warranted to improve professional performance in this area given the difficulty to diagnose CPNP by family physicians. The DN4 is a short diagnostic instrument that eventually could be used in everyday clinical practice, and we encourage more feasibility studies of its future use.

Conclusions
Chronic NP is a rather common health problem in primary care patients, and this first rural Italian primary care study, using the short diagnostic tool DN4, shows a prevalence of 0.77% with the two most common etiologies being diabetes NP and postherpetic NP.

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Conflicts of interest
There are no conflicts of interest.
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