

Systematic Review

Neuropathic Pain in Acute and Subacute Neuropathies: A Systematic Review

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Background: Neuropathic pain (NP) is a common symptom caused by lesions or diseases of the somatosensory nervous system. Acute/subacute peripheral neuropathies (APN) are rare, however can be particularly painful.

Objectives: The aim of this systematic review was to estimate the incidence of NP in APN and overview the various etiologies of such neuropathies.

Study Design: Systematic review.

Setting: Medline search.

Methods: We hand-searched Medline for observational studies published between 1995 and 2017.

Results: Our search strategy identified 1,400 papers. Of these, 70 met our inclusion criteria and were included in this review. Out of a total of 2,341 patients, 1,139 patients were diagnosed with NP (pooled incidence of NP 48.7%). In Guillain-Barré syndrome (GBS), the commonest cause of APN, the pooled estimate of NP was 34.8%. Other causes of painful APN include immune-mediated, vasculitic, metabolic, nutritional, toxic, paraneoplastic, and infectious.

Limitations: An important limitation was that GBS accounted for the majority of patients with APN, as such the calculated incidence reflected mainly this disease entity. Another important limitation was that very few studies targeted primarily NP. Thus, it is highly likely that observational studies reporting NP were missed. Finally there could always be a publication bias due to underreporting and gray literature.

Conclusions: NP is a cardinal manifestation of APN. The use of validated diagnostic tools and accepted diagnostic criteria of NP is recommended for both clinical and research purposes.

Key words: Neuropathic, pain, acute, subacute, neuropathy, polyneuropathy, frequency, incidence

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Neuropathic pain (NP) is estimated to affect 6-8% of the general population in Europe causing poor general health and low quality of life (1). The International Association for the Study of Pain defines NP as "pain initiated or caused by a primary lesion or dysfunction in the nervous system" (2). Treede et al (3) in 2008 proposed a different definition of NP as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system." In

general, NP can be caused by lesions of the central or the peripheral nervous system, or both, and may be acute, subacute, or chronic (4,5).

The diagnosis of NP remains principally clinical and it is based on the detection of both dysesthesias (i.e., burning, cold, pricking, shooting, electric shock-like, tingling, itching, pins and needles, stabbing, lancinating, and other painful sensations) and negative symptoms (i.e., numbness, hypoesthesia, anesthesia,

etc.) (5). Hyperalgesia (i.e., increased pain in response to a painful stimulus, e.g., by a pin, painful heat, or cold) and allodynia (i.e., pain in response to a nonpainful stimulus, e.g., thermal, vibration, mechanical static pressure, or mechanical dynamic moving light touch) are pathognomonic symptoms of NP, reflecting excessive activity of the sensory system due to a lower threshold or excessive activity (5).

Despite the importance of the clinical diagnosis of NP, the need for consistency among health professionals has led to the adoption of several "objective" screening tools of NP. Examples are the McGill pain questionnaire (or its short form) (6,7), the neuropathic pain scale (8), the neuropathic pain symptom inventory (9), and others (e.g., Pain Detect, ID-Pain, DN4 -douleur neuropathique- and LANSS pain scale - Leeds assessment of neuropathic symptoms and signs) (5,10).

Causes of painful peripheral neuropathies are numerous, however, occasionally patients might suffer from idiopathic (of unknown etiology) painful neuropathies (11,12). This article focuses solely on acute and subacute peripheral neuropathies. The primary aim of this systematic review was to explore the incidence of pain in such neuropathies. We also aimed to overview the causes of acute and subacute painful peripheral neuropathies.

METHODS

We hand-searched MEDLINE for articles published since January 1, 1995 using English language restrictions (last search in June 2017). The search strategy included the following keywords: "pain OR painful OR neuralgia," "acute OR subacute," and "neuropathy OR polyneuropathy OR polyradiculopathy OR neuronopathy OR neuritis OR mononeuritis OR ganglionopathy OR guillain-barré OR Miller-Fisher." Only observational studies were included (i.e., cohorts, case-control, cross-sectional, case series, and case reports) after careful screening of titles, abstracts, or full-texts. Articles referring to children, mononeuropathies, monoradiculopathies, traumatic, or ischemic neuropathies were excluded (e.g., carpal tunnel syndrome and other entrapment neuropathies, post-herpetic neuralgia, ischemic monomelic neuropathy after hemodialysis, etc). Articles with vague definitions of pain, not specifying if it is NP or not, were also excluded to avoid bias. The literature search and the study selection were independently conducted by both authors. We also perused the reference lists of the papers in order to find papers not found through the above mentioned search strategy.

Data extraction included the following characteristics: disease type, sample size, demographics (age and gender), incidence of NP, method of NP diagnosis, and definitions of "acute" and "subacute". The incidence of NP was derived by studies with more than 10 patients.

RESULTS

Search Results

The search strategy resulted in 1,400 articles. After eligibility assessment, 70 articles met our inclusion criteria. Of these, 29 were identified as observational studies of more than 10 patients reporting on the incidence of NP. The other 41 were case reports or small case series studies.

Incidence of NP in Acute/Subacute Neuropathies

A total of 2,341 patients (1,108 women and 1,233 men, mainly middle-aged) with acute/subacute neuropathies were described in the studies (13-41). The majority of the patients had Guillain-Barré syndrome (GBS) (1,529 of 2,341, 65.3%). In total, 1,139 patients were diagnosed with NP (pooled incidence 48.7%). The disease-specific NP incidence was: GBS or Miller-Fisher syndrome (MFS) 34.8%, (range: 9.6%–85.5%), treatment-induced peripheral neuropathy of diabetes (TIND) 100%, diabetic cervical/lumbar radiculo-plexopathy 86.4% (range: 81.2–100%), acute chemotherapy-induced peripheral neuropathy (ACIPN) 85% (range: 56.3–88.5%), Sjögren 12%, Churg-Strauss syndrome (CSS) 94.9% (range: 81.8–100%), nonsystemic vasculitic neuropathy (NSVN) 60%, infections 41.2%, toxic 100%, acute autonomic and sensory neuropathy (AASN) 95.2%, post-surgical neuropathy (PSN) 85.7%, acute nutritional neuropathy (ANN) 100%, and acute/subacute paraneoplastic neuropathy 75%. Table 1 summarizes the characteristics of the studies used for calculating the incidence of NP in acute/subacute neuropathies.

Causes of Acute/Subacute Painful Neuropathies

Common causes of acute/subacute neuropathies are reported below (13-41). Rare causes of acute/subacute neuropathies are summarized in Table 2 (42-82).

Immune-mediated Acute/Subacute Neuropathies

GBS is an acute immune-mediated polyradiculoneuropathy causing acute weakness and disability in affected patients. The types of pain in GBS include

Neuropathic Pain in Acute and Subacute Neuropathies

Table 1. *Observational studies of patients with acute neuropathies and the incidence of neuropathic pain.*

Reference	Disease (Number of patients)	Demographics (age in years old, Women/Men ratio)	Definition of acute/subacute	Sensory assessments	Incidence of Neuropathic Pain
13)	GBS (541)	Mean 41.6 ± 15.3 210/331	Days (vague)	Clinical	52/541
14	Pure motor GBS Europe: 225 Curacao: 83	Europe: Median 55 (20-74) 95/130 Curacao: Median 44 (6-71) 33/50	≤1 month	Clinical, EPT	123/225 39/83
15	GBS (223)	Median 50 123/130	≤1 month	Nonvalidated self-reported questionnaires	123/223
16	GBS (156)	Median 50 (35-63) 61/95	≤3 weeks after onset	Clinical MPQ, NRS, EPT	43/152
17	GBS (110)	Median 49.6 (IQR 16.7) 68/42	24hr after admission	Clinical, nonvalidated questionnaire, EPT	30/110
18	GBS (55)	Mean 50.6 21/34	On admission	Clinical, NRS, MPQ	47/55
19	GBS (42)	Mean 52 ± 18 (20-80) 18/24	≤2 weeks	Clinical, NRS	30/42
20	GBS/MFS (32)	GBS: 52 ± 15 MFS: 54 ± 17 13/19	≤3 weeks	Clinical, Unknown questionnaire, NRS, SB	14/32
21	GBS (30)	Mean 59.3 ± 17.2 (21-81) 14/16	Within days after admission	Clinical, BPI, DN4, MPQ, NPSI, QST, EPT	13/30
22	GBS (24)	Mean 51 (16-84) 14/10	During hospitalization	Clinical, Nonvalidated pain questionnaire, EPT	14/24
23	Mild GBS ¹ (12)	Median 52 (19-64) 5/7	At presentation	Clinical, EPT	7/12
24	MFS (27)	Median 38 (10-75) 14/13	At Presentation	Nonvalidated questionnaire	6/27
25	TIND (104)	DM1: Mean 25 ± 6.7 DM2: Mean 50.9 ± 6.8 73/31	≤8 weeks	Clinical, NIS, EPT, NRS	104/104
26	TIND (summary of 34 cases)	Mean 47.7 13/14	n/a	Clinical, EPT	34/34
27	TIND (16)	Mean 34.6 (19-58) 9/7	n/a	Clinical, NIS, NRS, SB	16/16
28	DCRPN (85) and DLRPN (33)	Median 62 (51-66) and Median 65 (60-71) 29/56 and 13/20	Acute: ≤24hr Subacute: 1day-1month	Clinical, EPT, QST,NB	69/85 and 33/33
29	ACIPN (86)	Median 56 (26-74) 30/56	Within 24hrs after oxaliplatin	Clinical, nonvalidated interview	75/86
30	ACIPN (81)	Mean 60.5 (33-89) 60/21	≤7 days after paclitaxel infusion	Nonvalidated Questionnaire	69/78
31	ACIPN (16)	Mean 64.6 ± 12.4* 11/5	After oxaliplatin infusion	MPQ, QST	9/16
32	Sjögren (92)	Mean 58.1 ± 15.9* 76/16	Symptoms present for days or weeks	Clinical, EPT, NB	11/92
33	NSVN (60)	Median 64 (24-80) 21/39	Admission	Clinical, NSS, NDS, EPT, NB	36/60

Table 1 (cont.). *Observational studies of patients with acute neuropathies and the incidence of neuropathic pain.*

Reference	Disease (Number of patients)	Demographics (age in years old, Women/Men ratio)	Definition of acute/subacute	Sensory assessments	Incidence of Neuropathic Pain
34	CSS (28)	Mean 52.4 (22-78) 22/6	≤1 week	Clinical, EPT, NB	28/28
35	CSS (11)	Mean 53 (45-63) 6/5	Acute: ≤1 month, Subacute: 1-3 months	Clinical, EPT	9/11
36	Tick borne encephalitis and Lyme borreliosis (51)	n/a	At presentation	Clinical	21/51
37	Toxic ^s (24)	Median 33 (20-54) 14/10	n/a	Clinical, EPT, QST, NB	24/24
38	AASN (21)	Mean 29 ± 14.9 15/6	≤1 month	Clinical, EPT, NB	20/21
39	PSN (21)	Median 65 (24-83) 11/10	≤1 month	Clinical, NIS, EPT, QST, NB	18/21
(0)	ANN (13)	Mean 37 (16-54) 13/0	Acute: ≤4 weeks Subacute: ≤12 weeks	Clinical, NRS, EPT, NB, SB	13/13
41	Paraneoplastic (Hu and some CV2 positive) (12)	Median 64 (42-80) 3/17	Acute: ≤1 month Subacute: 1-6 months	Clinical, EPT	9/12

*Data for patients with neuropathic pain only.

§Exposure to aerolised brain tissue during pig carcasses' processing in US abattoirs

AASN: Acute Autonomic and Sensory Neuropathy, ACIPN: Acute Chemotherapy Induced Peripheral Neuropathy, ANN: Acute Nutritional Neuropathy, BPI: Brief Pain Inventory, CSS: Churg Strauss Syndrome, DCRPN: Diabetic Cervical Radiculoplexus Neuropathy, DLRPN: Diabetic Lumbar Radiculoplexus Neuropathy, DN4: Douleur Neuropathique, EPT: Electrophysiology tests (i.e., nerve conduction studies with or without electromyography), GBS: Guillain-Barré syndrome, MFS: Miller-Fisher Syndrome, MPQ: McGill Pain Questionnaire, NB: Nerve biopsy, NDS: Neurological Disability Score, NIS: Neuropathy Impairment Score, NPSI: Neuropathic Pain Symptom Inventory, NRS: 11-point numeric rating scale for pain intensity or visual analog scale 0-10 cm, NSS: Neurological Symptom Score, NSVN: Non-Systemic Vasculitic Neuropathy, PSN: Post-surgical Neuropathy, QST: Quantitative Sensory Testing, SB: skin biopsy, TIND: Treatment-induced Neuropathy of Diabetes, n/a: not available

Table 2. *Rare causes of acute neuropathy presenting with neuropathic pain.*

Vasculitic neuropathies
Polyarteritis Nodosa (42)
SLE (43,44)
Wegener's granulomatosis (45)
Sarcoidosis (46)
Infectious neuropathies(e.g., herpetic, rickettsiosis, West Nile, HIV) (47-51)
Toxic neuropathies (e.g., antiretroviral drugs, metronidazole, fluoroquinolone, minocycline, rabbit antithymocyte globulin, heroin, fish poisoning, thallium, organophosphate poisoning) (52-61)
Primary neurolymphomatosis (in non-Hodgkin lymphoma and leukemia) (62-66)
Rare paraneoplastic acute neurological syndromes (67,68)
Critical illness polyneuropathy (69,70)
Acute branchial neuritis (Parsonage-Turner Syndrome) (71-77)
Erythromelalgia (78,79)
Subacute peripheral and optic neuropathy syndrome (80,81)
Hereditary motor and sensory neuropathy (MPZ mutation) (82)

peripheral NP, radicular pain, meningism, headache, muscular pain secondary to bad posture, visceral pain, and arthralgias (13-24,83). Pain can be acute, subacute, or chronic and it may appear in all GBS variants (e.g., mild GBS, pure motor GBS, pure sensory GBS, etc), albeit patients with MFS tend to show significantly reduced incidence of acute neuropathic pain (84). Although NP in GBS is usually not among the first manifestations, in some cases it can precede or coincide with weakness. Interestingly, pain in GBS was more conspicuous in patients with nerve root enhancement in magnetic resonance imaging (MRI) compared to patients with no enhancement (22).

AASN is a rare entity causing monophasic variable autonomic and sensory disturbances with a peak severity during a short period of time, usually preceded by an infection (38). This is primarily an axonal neuropathy of unmyelinated and mainly small myelinated nerve fibers, explaining the lack of motor symptoms in these patients. Also, the wide distribution of sensory and autonomic symptoms and signs resemble that of a ganglionopathy affecting both sensory and autonomic ganglia. Further support of a ganglionopathy is rendered by the sparing of motor function despite the late appearance of symptoms and signs indicative of deep sensory impairment. Some authors consider this entity as a variant of GBS (pure sensory type) in the light of similarities concerning the rapid clinical progression, preceding infection, albuminocytologic dissociation, and response to intravenous immunoglobulin (38).

PSN is an acute inflammatory neuropathy occurring within one month after surgery that cannot be attributed to mechanical factors (e.g., compression neuropathy). It is a sensorimotor axonal neuropathy manifested as polyradiculopathy, plexopathy, polyneuropathy, or mononeuropathy. The clinical course is benign with symptoms abating with or without immunosuppressive therapy (39).

With respect to the pathogenesis, NP has been associated with damage of the small unmyelinated nerve fibers carrying thermal and nociceptive sensation as attested by low intraepidermal nerve fiber density (IENFD) in skin biopsies (20). Notably, NP in GBS can exist without clinical evidence of sensory symptoms or signs and sensory nerve abnormalities in nerve conduction studies (NCS), which makes it difficult to differentiate by other types of pain. In these occasions, NP has been attributed to nociceptive activation of the nervi nervorum of the motor nerves by inflammatory mediators, or spontaneous discharges of dying motor axons

in axonal GBS (14). However, low IENFD has been linked to both increased NP incidence and severity, even in patients with pure motor GBS (20). Neck and/or back pain have been imputed to swollen nerve roots and muscle pains or changes in muscles of neurogenic origin (i.e., activation of the muscles' nociceptive receptors due to increased dying motor neurons discharges) (42). Finally, increased intracranial pressure has been observed in GBS patients causing headache and meningism (43).

Diabetes Related Acute/Subacute Neuropathies

TIND (also known as "insulin neuritis") is an acute painful neuropathy occurring within about 2 months after rapid correction of serum glucose or a decrease above 2% of glycosylated haemoglobin (HB1ac) per 3 months, with insulin or oral hypoglycemic agents after a long history of hyperglycemia (25-27). Pain initially affects distal limbs or even abdomen and rapidly generalizes to affect the whole body (25-27). Pain is accompanied by autonomic symptoms (e.g., syncope, orthostatic hypotension, early satiety, constipation, diarrhea, hypohidrosis, hyperhidrosis, etc.) suggesting a small fiber pathology (25-27). Interestingly, larger decrements of HB1ac have been associated with more widespread body surface area affected by pain and more severe autonomic dysfunction (25). It is usually a self-limited condition often taking many months before full improvement. NCS's reveal axonal mainly sensory, but also motor neuropathy (25-27). The pathogenesis of TIND remains elusive. Mechanisms such as endoneurial ischemia due to a "steal effect" by proliferating new vessels and arteriovenous shunting in the epineurium, microvascular changes due to recurrent hypoglycemia, apoptosis in the dorsal root ganglia due to glucose deprivation, and accelerated regeneration of small fibers producing ectopic discharges, have been postulated (25).

Diabetic cervical plexopathy and diabetic lumbosacral plexopathy usually occur independently and are unilateral; however, simultaneous presentation of 2 plexopathies has been reported. Both syndromes are mostly monophasic characterized by acute or subacute pain, weakness and weight loss, all leading to transient disability. Axonal ischemic injury due to microvasculitic changes is the main pathological finding in biopsies of the affected nerves (28). The role of the immune system in the pathogenesis of these disorders is still debatable.

Cancer Related Acute/Subacute Neuropathies

ACIPN presents immediately after administration of

the chemotherapeutic drug (e.g., oxaliplatin, paclitaxel) and is characterized by NP starting mainly in the hands, feet, or face, with cold sensitivity and cold-induced pain (indicating mainly A δ fiber damage) being the most commonly reported symptom by over 80% of patients (29-31). The incidence of pain and its duration increase with larger cumulative doses of the chemotherapeutic drug (85). Other risk factors for ACIPN are genetic polymorphisms, pre-existing peripheral neuropathy, history of smoking, and decreased creatinine clearance (85). The pathogenesis of this dose-dependent neurotoxicity is not clear; however, ion conductance anomalies and apoptosis of cells in the dorsal root ganglia have been proposed (85).

Primary neurolymphomatosis, a rare manifestation of non-Hodgkin lymphoma and leukemia, is caused by infiltration of the peripheral nervous system by cancer cells (62-66). Positron emission tomography and nerve biopsy may assist the diagnosis.

Paraneoplastic neurologic syndromes (PNS) are a heterogeneous group of disorders caused by mechanisms other than metastases, metabolic and nutritional deficits, infections, coagulopathy, or side effects of cancer treatment. These syndromes may affect any part of the nervous system from cerebral cortex to neuromuscular junction and muscle. The immunologic response is directed against shared antigens that are ectopically expressed by the tumor, but otherwise exclusively expressed by the nervous system. Subacute sensory neuronopathy (or Denny-Brown syndrome) causing severe widespread pain belongs to the "classical syndromes" meaning that there is strong evidence in favor of concomitant or impending cancer (41). Hu and CV2 antibodies are well-characterized antibodies associated with subacute sensory neuronopathy (41). Pain is very prevalent in paraneoplastic sensory ganglionopathies as it can affect up to 60% of patients during the course of the PNS. Pain is among the first symptoms of the paraneoplastic neuropathy in more than 40% of the patients and it can be the sole first manifestation of the paraneoplastic neuropathy in 13% of the patients (86,87).

Vasculitic Neuropathies

Vasculitic neuropathies manifest with pain of abrupt onset and weakness of the muscles innervated by the nerve which is affected. Electrophysiologically vasculitic neuropathy is characterized by an asymmetrical, nonlength dependent sensorimotor axonal degeneration, however with time, accumulation of

many mononeuropathies might mimic a symmetrical polyneuropathy making diagnosis more challenging (32-35).

Systemic symptoms (e.g., fever, weight loss, increased inflammatory markers and organ-specific symptoms, or abnormal laboratory studies) may further assist diagnosis of the underlying cause. In the nonsystemic vasculitic neuropathies, the systemic manifestations are more negligible and only nerve and/or muscle biopsy showing necrotizing inflammation of the vasa nervorum can establish the diagnosis.

Acute/subacute Neuropathies Due to Deficiencies

ANN is an acute/subacute sensory or sensorimotor length-dependent axonal neuropathy preceded by weight loss, vomiting, and nutritional derangements due to alcohol abuse, bariatric surgery, or other dietary problems (40). Sensory small fiber involvement may account for NP in these cases. Distinction between ANN and GBS can be made on the basis of onset for many days or weeks, lack of preceding infection, absence of cranial nerve involvement and respiratory compromise, and negative anti-ganglioside antibodies. Thiamine deficiency may be the major culprit for this disorder.

Subacute peripheral and optic neuropathy syndrome occurs mainly in metabolic disorders (e.g., B12 or folic acid or copper or thiamine deficiency) and alcoholism. Genetic susceptibility to the syndrome involving mitochondrial DNA mutations is strongly suspected (80,81). The syndrome is characterized by a predominantly sensory distal symmetric painful neuropathy affecting the lower limbs more than the upper limbs. In some cases, marked ataxia denote concomitant ganglionopathy. Visual symptoms may precede or follow the peripheral neuropathy in a period of one month after onset, which is pathognomonic for the syndrome (80,81).

DISCUSSION

This systematic review included a total of 70 publications in order to calculate the incidence of NP in acute and subacute peripheral neuropathies of various etiologies.

This systematic review has a number of limitations. First of all, we searched only MEDLINE, thus there is a chance that some studies have been missed. Furthermore, a major limitation for NP incidence estimation was that GBS accounted for the majority of patients with acute neuropathies. It is, thus, more likely that the final incidence of NP would be influenced mostly by this disease entity. However, given that GBS is the most

frequent acute neuropathy, the estimated incidence gives the clinician a rough estimate of NP in acute neuropathies taking into account their frequency. Another important limitation was that very few studies targeted solely or primarily on NP, thus data on NP diagnosis and occurrence might be misleading. For the same reason, it is highly likely that we have missed observational studies reporting NP as part of the clinical characteristics of their clinical samples. Finally, there could always be a publication bias due to underreporting negative results and gray literature.

Our paper indicated the following key points:

1. The overall pooled incidence of NP in acute and subacute neuropathies is 48.7%. The disease-specific pooled incidence of NP showed that some acute/subacute neuropathies are almost always painful (such as the diabetes related) when others are affecting a smaller percentage of patients (such as in GBS). More observational studies reporting the incidence of NP in acute/subacute neuropathies of various etiologies are needed in order to have a clearer picture of the exact figures.
2. Adequate diagnosis of NP is lacking as not all studies reported how NP was defined or whether validated tools for the diagnosis of the neuropathic element of pain were used. Therefore, there is always a chance that any pain reported by some patients would be ascribed as NP by physicians, especially on the basis of an acute/subacute peripheral neuropathy diagnosis. Screening tools only offer guidance for further evaluation and they should not replace clinical judgment (5). On the other hand, clinical judgment of NP should adhere to a specified criterion-based context that would prevent arbitrary reporting.
3. The terms “acute” and “subacute” were used variably in the studies presented in this review.

“Acute” definitions ranged from 1 day to 8 weeks after symptom onset and “subacute” definitions ranged from 1 day to 3 months. In general, acute and subacute neuropathies characteristically cause symptoms that evolve quickly and start to abate (with or without therapy) within 4 to 8 weeks, respectively (2-5). However, some clinicians still use “acute” to describe a well-defined steep onset and/or severe symptoms. In our view, acute, subacute and chronic NP should correspond to both clinical and pathological evidence. In any case, there is a need for clearly defining the timeframes during which pain will be considered as acute, subacute, or chronic. As such, the terms hyperacute, acute, subacute, and chronic for NP implicating small sensory fibers (mainly C and A δ fibers), should be refrained for symptom onset within 24 hours (to address situations such as ACIPN and toxic neuropathies), 24 hours to one month (during which a growing number of axons is lost), 1–3 months (axon loss has been roughly maximized given that the first insult is absent and regeneration occurs), and over 3 months (3 months are considered the start of the normal healing period and skin reinnervation by surviving axons in sensory neuropathies, reaching its peak in 5–6 months), respectively (2-5,88).

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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