Painful Peripheral Neuropathies

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Abstract: Peripheral neuropathies are a heterogeneous group of diseases affecting peripheral nerves. The causes are multiple: hereditary, metabolic, infectious, inflammatory, toxic, traumatic. The temporal profile includes acute, subacute and chronic conditions. The majority of peripheral neuropathies cause mainly muscle weakness and sensory loss, positive sensory symptoms and sometimes pain. When pain is present, however, it is usually extremely intense and among the most disabling symptoms for the patients. In addition, the neurological origin of the pain is often missed and patients receive inadequate or delayed specific treatment. Independently of the disease causing the peripheral nerve injury, pain originating from axonal pathology or ganglionopathy privileges neuropathies affecting smaller fibres, a clinical observation that points towards abnormal activity within nociceptive afferents as a main generator of pain. Natural activation of blood vessels or perineurial nociceptive network by pathology also causes intense pain. Pain of this kind, i.e. nerve trunk pain, is among the heralding symptoms of inflammatory or ischemic mononeuropathy and for its intensity represents itself a medical emergency. Neuropathic pain quality rekindles the psychophysical experience of peripheral nerves intraneural microstimulation i.e. a combination of large and small fibres sensation temporally distorted compared to physiological perception evoked by natural stimuli. Pins and needles, burning, cramping mixed with numbness, and tingling are the wording most used by patients. Nociceptive pain instead is most often described as aching, deep and dull. Good command of peripheral nerve anatomy and pathophysiology allows timely recognition of the different pain components and targeted treatment, selected according to intensity, type and temporal profile of the pain.

Key Words: Pain, neuropathic, polyneuropathy, small fibres neuropathy, diabetic neuropathy, post herpetic neuralgia, paraneoplastic polyneuropathy, hereditary neuropathy.

INTRODUCTION

Peripheral neuropathies are hereditary or acquired diseases affecting the cell body of peripheral sensory or motor neurons, their axon, or myelin; they are clinically defined as *demyelinating* and *axonal*, or *neuronopathy* (when the cell body is affected), and classified into sensory, motor or autonomic. Peripheral neuropathies can be classified depending on their time course into acute, sub acute or chronic. They are also defined as polyneuropathies or mononeuropathy, which can be isolated or can spread to different sites (multiple mononeuropathy) according to the anatomical distribution of the sensory motor and autonomic loss.

Polyneuropathies are diseases affecting all peripheral nerves and typically heralding on the feet where fibres are the longest. Mononeuropathies affect peripheral nerves focally, beginning with symptoms at one site - usually a limb – and then spreading to a different site, with an asymmetrical pattern. When the disease causing mononeuropathy progresses, multiple nerves might be affected (multiple mononeuropathy) ending with a clinical picture quite akin to a polyneuropathy.

In polyneuropathies the disease affects primarily either axons or myelin or both. In mononeuropathy the disease affects usually the entire nerve trunk, particularly the connective neural tissue and nerve blood vessels, which are the primary pathophysiological target.

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Many peripheral neuropathies are painless and not all pain felt in diseases of peripheral nerves is neuropathic in nature.

The International Association for the Study of Pain [38] defines neuropathic pain as "Pain initiated or caused by a primary lesion or dysfunction in the peripheral or central nervous system". The inclusion of "dysfunction" in the definition of neuropathic pain may be confusing allowing the diagnosis of nociceptive and psychogenic conditions as neurogenic/neuropathic. We have defined neuropathic pain [23] as a "pain due to primary lesion of the peripheral or central nervous system", a definition that is now widely accepted [37, 4].

Pain and related neuropathic symptoms and signs may vary in relation to the temporal evolution of the painful disease, and to the mood and anxiety of the patient. Neuropathic pain can be spontaneous (i.e. stimulus-independent) with episodic or continuous temporal profiles. Neuralgias (such as the trigeminal and glossopharyngeal neuralgia) have characteristic episodic paroxysms, although other pains in neuropathy may appear as isolated attacks, or attacks of increasing intensity superimposed on a continuous pain. Spontaneous symptoms are described as uncommon tactile and thermal sensations associated with numbness, tingling, pins and needles, burning, shooting, and electric shock-like sensation. Neuropathic pain may also be evoked. The evoking stimulus may cause massive activation of ectopic sensory discharges by acting on mechanosensitive neural pathways as in the Tinel sign. Pain may also be evoked by natural stimulation of an abnormally sensitive area (stimulus-dependent pain) generating a sequence of spontaneous attacks, such as trigger

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points activation of tic douleureux, or remaining time locked with the percept, albeit with exaggeratedly intense or distorted quality evoking abnormal sensations such as allodynia or hyperalgesia.

Neuropathies affecting only motor nerves may cause painful cramps. This symptom is rare to absent in slowly evolving hereditary motor neuropathies, but is common in the rapidly evolving primary motor neuron diseases. Painful neuropathic cramps are likely originated by physiological activation of muscle nociceptors stimulated by repetitive voluntary activation of the surviving giant motor units or spontaneous high frequency discharges of the dying neurons. Both mechanisms may coexist in the same patient, and, in this particular case, cramps quickly respond to channel blocking agents.

Peripheral nerves might hurt when sensory afferents are abnormally active or when the entire nerve trunk is abnormally stimulated. Activity originating from sensory axons is a true neuropathic pain, while activation of nociceptors present in muscles, perineurium or nerve blood vessel during a disease of peripheral nerves, produces nociceptive pain [34].

Dysesthesia, hyperalgesia and allodynia are the terms applied to define the aberrant evoked sensory phenomena [30]. Sensitisation of nociceptors, ectopic activity and multiplication of impulses are likely peripheral mechanisms of dysesthesia and hyperalgesia [44]. Allodynia is a more complex condition. By definition the term implies a painful percept evoked by stimuli (mechanical or thermal) of intensity below the nociceptor threshold. Therefore, allodynia is widely recognised as the clinical "sign" of central sensitisation [64]. However, nociceptor threshold is remarkably lower than pain threshold, the pain percept requiring temporal and spatial summation of nociceptive impulses to overcome the endogenous inhibitory state. Thus, what common experience would reasonably define as a stimulus of painless intensity might be sufficient to activate nociceptors [36]. Hyperactivity and multiplication of discharges in peripheral nociceptive afferents may well give raise to allodynia. Novel recordings from nociceptors in patients with allodynia in painful neuropathies provide objective strength to this "peripheral" explanation [43].

Intraneural microstimulation in humans shows that in healthy subjects pain is felt when small fibres are stimulated. The pain quality such as burning, pins and needles, cramping etc. varies according to the stimulated axon. Stimulation of large fibres evokes sensations other than pain such as tingling [45]. Patients affected by peripheral nerve disease complain of abnormal spontaneous and evoked sensations and sensory loss. The qualities of the spontaneous abnormal sensations described by patients rekindle the experience of intraneural microstimulation. Abnormal sensations originating from large fibres such as intense tingling and buzzing in fingers and toes might certainly be unpleasant, albeit it is hard to define them as pain. Abnormal sensations with a pain quality appear as a rule jointly with loss of sensation subserved by small fibres.

Pain and sensory loss often have a different temporal profile; pain usually is at its worst intensity in the early stages while sensory loss worsens progressively later. In some severe polyneuropathies, pain might even subside when there is severe hypoesthesia. Pathological conditions attacking the nerve from outside, as compression, ischemia or inflammation, might cause pain of nociceptive type, i.e. nerve trunk pain, and subsequently also nerve damage with clear-cut neuropathic pain. Perineurium nerves (nervi nervorum) play initially the role of any sensitive structure while after injury the bundle of nerve fibres may become itself generator of abnormal neural impulses. Under these conditions, nociceptive pain may be the heralding symptom and it is often an extremely intense deep and aching pain, lasting for days, rarely more than two weeks. The neurological symptoms and signs appear when the nerve injury involves the axons, and this is often some days after the beginning of the pain depending on the aetiology of the injury and the speed of progression.

For the somatotopical organization of the peripheral and central nervous systems, all neuropathic pains are perceived within the innervation territory of the damaged structure. A neuro-anatomical distribution of pain and sensory alteration supports the diagnosis [23] that relies on the medical history and bedside examination. The evaluation aims at correlating sensory, motor and autonomic signs with the detailed medical history.

Autonomic signs as cold or hot limbs may be a direct consequence of the nerve injury, or a spinal/supraspinal reflex to the nociceptive input; care should be taken to disentangle these phenomena avoiding unuseful treatments [5]. Electromyography, nerve conduction studies, evoked potentials, infrared tele-thermography and quantitative sensory testing support the clinical diagnosis allowing better definition of nerve fibres or central sensory pathways involved.

In addition to mononeuropathy, nociceptive nerve pain is felt also in radiculopathy due to disc compression and osteoarthritis or inflammation, in the acute brachial (Parsonage and Turner) or lumbar plexopathy, and in the demyelinating polyradiculoneuropathy (Guillain Barré syndrome). In plexopathy, pain might be a medical emergency by itself, before neurological signs appear. In the acute polyradiculoneuropathy, pain might shortly herald the explosion of the disease and it is typically localised in the back, coinciding with the anatomical location of the affected rootlets. At times nociceptive nerve pain and neuropathic pain coexist and last together for a long time. In carpal tunnel syndrome there is often a combination of focal nociceptive pain in the wrist, and neuropathic projected sensory disturbances and pain in the fingers. Radiculopathy in spondyloarthritis also often combines nerve trunk pain in the back and neuropathic pain in the radicular sensory territory. In contrast, in peripheral neuropathy associated with leprosy the axonal damage usually causes painless sensory loss, while the pain is nociceptive, due to the combination of nerve inflammation and entrapment.

A comprehensive epidemiology of painful peripheral neuropathies is not yet available [56], although, as a whole, pain is a relevant problem in peripheral nerve diseases and injury, because of its frequency and resistance to treatment.

There is information on prevalence and incidence of some peripheral nerve diseases; however, the same neuropathy may be painful in some cases and painless in others. This is typically the case of posttraumatic nerve injury that is painful in less than 10% of the cases [59]. The most common painful neuropathies are diabetic neuropathy and postherpetic neuralgia, for which epidemiological data are available [7, 33, 49].

In describing the clinical classification of painful peripheral neuropathies we begin with hereditary neuropathies, which are seldom painful but are of great interest because they allow a correlation between the involvement of selective nerve fibres and the presence of pain.

HEREDITHARY NEUROPATHIES

Hereditary neuropathies are heterogeneous conditions sharing the genetic cause of the disease. In most of the cases, they evolve slowly over many years, with a severity ranging from mildly disturbing to invalidating. As a group, hereditary neuropathies are common disorders, and likely many patients affected by mild forms remain undiagnosed [46]. Hereditary neuropathies may affect predominantly motor fibres, or sensory and motor fibres or sensory and autonomic fibres. The genetic abnormality may involve primarily the myelin or the axon. The chief complaint in hereditary sensory-motor demyelinating neuropathies is usually weakness. Patients also complain of numbness that is a positive sensory phenomenon originating from spontaneous large fibres activity. Sensory loss preferential for low threshold mechanical stimuli is more often a clinical finding than a spontaneous complaint. Sensory demyelinating neuropathies provide clinical evidence against the inhibitory role of large peripheral nerve afferents proposed by the gate control theory. In demyelinating sensory neuropathies small fibres are spared, and there is no loss of pain sensation. Contrary to what one would have expected if activity in large fibres had inhibitory effect on small fibres input, there is not spontaneous pain or hyperalgesia.

The few hereditary polyneuropathies that are painful primarily affect small fibres. The hereditary sensory and autonomic neuropathies with abnormality in the axonal structure are subdivided in five groups. The latter three groups (III, IV and V) have clinical expression already at birth. In these severe unmyelinated axonal neuropathies there is insensitivity to pain and major dysautonomia, often incompatible with survival. The hereditary sensory and autonomic neuropathy type II shows clinical symptoms in the infancy, there is loss of pain and warm sensation to such extent that hands, feet and tongue are at risk of spontaneous or traumatic mutilation. In this neuropathy, spontaneous pain is not a chief complaint. In the hereditary sensory and autonomic neuropathy type I, which has clinical manifestation of small fibres sensory loss, leading to cutaneous ulcers and spontaneous stress fractures around the second decade of life, severe lancinating pain is the main complaint. Thus, the hereditary small fibres sensory neuropathy is painful in adults, but not in neonates, a condition rekindling the effects of capsaicin treatment in neonates and adult mice [53, 25]. Small sensory and autonomic fibres are affected in other hereditary diseases in which the genetic abnormality leads to accumulation of substances in or around small neurons of sensory and autonomic ganglia. Two such conditions are known for being particularly painful: Fabry's disease and familial amyloid neuropathy.

Fabry's disease is an X-linked recessive disorder in which there is deficiency of the lysosomal enzyme galactosidase, causing accumulation of glycolipids in small neurons. Accumulation of glycolipids causes association of kidney, myocardial, and brain disease. It is a painful small fibres neuropathy developing in childhood or adolescence. Lancinating burning pains are intensified by exertion, and hot environment likely related to a state of hyperalgesia to those stimuli. There is concomitant loss of autonomic fibres causing anhydrosis, impaired saliva and tear formation, decreased intestinal mobility and hypotension. The presence of severe burning pain with causalgic quality in people with complete loss of autonomic fibres provides also a case against a role of the sympathetic system in contributing to the pain, at least in this population of patients.

Familial amyloid neuropathy is a group of autosomal dominant disorders with extracellular deposition of amyloid in peripheral nerves and other organs. Amyloid is composed by many different types of fibrillar proteins [17]. The classification of amyloidosis, which was previously based on the clinical presentation, now relays on the protein composition and molecular genetics. The original description of familiarity was made in Portugal (Andrade). In this neuropathy a mutation of the plasma protein transthyretin is found. It is the most common form of familial amyloidosis. The neuropathy begins insidiously around the age of 30 – 40 combining sensory loss for warm and pain, and spontaneous lancinating pain. There is also autonomic dysfunction. Treatment with enzyme replacement therapy improves pain to the extent that other pain medications can be discontinued [54].

Further understanding on the mechanism of action of enzyme replacement therapy on abnormal nociceptive activity in Fabry's disease might shed light on the treatment of other small fibres painful neuropathies.

Porphyric neuropathy is also a painful hereditary disease, usually autosomal dominant with incomplete penetrance, and occasionally autosomal recessive, which affects peripheral nerves, central nervous system and also the gastrointestinal and cardiovascular systems. In Porphyric neuropathy there is a defect of the heme synthesis resulting in excessive accumulation of porphyrins and their precursor. The typical clinical presentation appears as episodes of abdominal pain, nausea, vomiting and severe constipation. There might be tachycardia and orthostatic hypotension. Some patients may have epileptic seizures due to central nervous system involvement. The neuropathy may have the feature of a distal sensory neuropathy with proximal and asymmetrical muscle weakness. At times the sensory loss affects the trunk and proximal limbs. Pain used to be explained as a symptom of dysautonomia. In reality pain anticipates signs and other symptoms of neuropathy, last for a few days, and improves when the neuropathy becomes clinically evident. It is most likely a nociceptive type of pain due to ischemia of nerve trunks that

ultimately causes the neuropathy. This also explains the quite frequent asymmetrical and proximal distribution of sensory motor signs, typical of a multiple mononeuropathy [57].

ACQUIRED NEUROPATHIES

Weakness of limb and respiratory muscles is the paramount clinical feature of Guillain Barré, an autoimmune polyradiculoneuropathy related in about two thirds of patients to a preceding upper respiratory or gastrointestinal infection. Around 40% of patients worldwide and almost 80% in China have serological evidence of exposure to Campylobacter jejuni. Without respiratory assistance Guillain Barré polyradiculoneuropathy was fatal in almost a third of the patients; currently the mortality rate is around 5-10 % [60]. According to Moulin *et al*. [40], 85% of patients report moderate to severe pain mainly appearing at the onset of the motor symptoms. Pain is of two kinds: the most common is stabbing deep dorsal of low back pain, radiating into the limbs. Half of the patients report dysesthetic extremity pain with burning or tingling quality; a smaller number of patients report joint and muscle pain. It is likely that the back pain at onset is of nociceptive type and it is related to the radicular inflammation, while the distal extremity pain is neuropathic. The symptom of tingling originates from large myelinated fibres and when intense it may be defined as a dysesthesia. Burning is a less common symptom originating from small fibres; it might be caused by autoimmune aggression towards the unmyelinated axons, a rare case in Guillain Barré, or by a cross talk between all fibres type exposed to contact by the inflammation. Joint and muscle pain could be of neuropathic origin due to ectopic activity in nociceptive afferents subserving these tissues.

Ganglionopathies or sensory neuronopathies are conditions in which the primary target is the sensory ganglion. The most common is caused by herpes zoster infection. Herpes zoster almost constantly causes an acute neuralgia at the onset of inflammation. The acute pain is mediated by nociceptive and neuropathic mechanisms. Neuropathic pain is projected into the innervation territory of the sensory ganglion; the nociceptive pain is felt deeply in the paraspinal location of the ganglion. After recovery from the acute phase that happens within a few weeks, a long lasting neuropathic pain might take over. This pain, arising or persisting in areas affected by herpes zoster at least three months after healing of the skin lesion, has been defined as post herpetic neuralgia [50]. Post herpetic neuralgia may last for many years, sometimes for the whole life. It causes a most disabling pain that combines spontaneous and evoked pain. The sensory examination reveals areas of major, even complete sensory loss and areas of increased sensitivity (hyperalgesia or allodynia) to many different stimuli, particularly light stroking and warming. Pain in the area of sensory loss is caused by deafferentation of second order neurons, while evoked pain is caused either by irritable nociceptors or by sensitisation of central afferents [18]. This observation supports the hypothesis that one disease causing peripheral nerve injury might cause pain through more than one mechanism. Post herpetic neuralgia is easy to diagnose and has relatively high prevalence [22] among the different painful neuropathies; for this reason, post herpetic neuralgia is commonly studied in clinical trials on neuropathic pain.

PAINFUL PERIPHERAL NEUROPATHIES IN CANCER

Cancer may cause paraneoplastic polyneuropathy that is due to the toxic activity of cancer cells, or to an autoimmune response induced by cancer. The majority of paraneoplastic neuropathies are sensory, motor, axonal, or axonal and demyelinating polyneuropathies and they are seldom painful. Symptoms of paraneoplastic polyneuropathy often anticipate the symptoms of cancer. When symptoms of polyneuropathy appear in patients with diagnosed cancer they are more likely caused by chemotherapy. The mechanisms producing nerve injury, and in particular neuropathic pain and sensory symptoms, are not clear. However, the severity of nerve damage appears to be directly proportional to drug dosage [2, 9, 12, 29]. The widely used paclitaxel is known to provoke neuropathic pain and sensory dysfunctions mostly affecting hands and feet, related to a myelinated fibre neuropathy preferentially affecting the largest fibres, with sparing of C-fibres function at warm sensory testing [12]. Ascending distal paraesthesiae and dysesthesiae together with burning pain and allodynia to cold or mechanical stimuli in a stocking and glove-like distribution often appear after chemotherapy [62]. This finding of symptoms of small fibber neuropathy appearing in patients with predominantly large fibre sensory loss is contradictory with the evidence provided by the hereditary neuropathy that are painful when small fibre involvement prevail. However, in isoniazid polyneuropathy, the sparing of small fibres is apparent and compulsive analysis of small fibre histogram shows a shift towards the left with increased number of small diameter axons, indicating loss of main small fibres and production of regenerating smaller sprouts [42]. In addition, there is no doubt that myelinated fibres are affected by chemotherapy because vibration, pin and cold perception are impaired. However, it is possible that small-fibre type of positive symptoms (i.e. burning and cramping) anticipate the negative manifestation of sensory loss. In vincristine-induced polyneuropathy a small percentage of C-nociceptors respond in an exaggerated fashion to supra threshold heat stimulation [47]. Although modifications in threshold and spontaneous activity were not found in those cells, the finding supports a small-fibre generator of pain.

Cisplatin causes mainly large fibre neuropathy leading more often to painless ataxia, and vincristine also causes large fibres sensory motor neuropathy. Pain caused by the use of these agents is relatively rare and has the quality of a muscle pain, and may be more related to a direct muscle toxicity [21]. Patients with pre-existing neuropathy of any kind are more prone to develop polyneuropathy while on chemotherapy [11, 28], therefore, Sommer recommends to screen peripheral nerve function before initiating potentially neurotoxic chemotherapy [56].

Cancer patients often suffer also from painful invasion of peripheral nerves and plexus by cancer or from iatrogenic nerve injury, either due to radiotherapy or surgery [35]. Acute sensory polyganglionopathy is a rare autoimmune or paraneoplastic neuronopathy affecting sensory and autonomic ganglia. The neurological syndrome anticipates the diagnosis of cancer in 90% of the patients. The most common cancer associated with acute polyganglionopathy is the small-cell lung cancer; in rare cases polyganglionopathy is associated

with ovarian cancer, breast carcinoma or lymphoma. Giving the high specificity (99,8%) and sensitivity (82%) of the anti-Hu antibodies [39] in patients with no evidence of cancer, a CT study of the chest should be performed. The neuropathy causes major sensory loss for all sensory modalities with ataxia of lower and even upper limbs and loss of thermal sensation. Sensory loss rapidly involves the face and trunk, indicating direct neuronal cell involvement rather than axonal death. Pain is extremely intense, with stabbing and burning quality. Although paraneoplastic sensory neuropathy is related to an inflammatory, probably immune-mediated lesion of sensory neurons, usually it does not respond to plasma exchange, intravenous immunoglobulines, or immunosuppressants, but to the early treatment of the tumour [51].

NEUROPATHIC PAIN IN CONNECTIVE TISSUE AUTOIMMUNE DISEASES

Rheumatoid arthritis and Sjögren syndrome are the most common inflammatory connective tissue disease, affecting together more than 2% of the population [61]. Systemic lupus erythematosus, polyarteritis nodosa, Churg-Strauss syndrome, microscopic polyangiitis, Wegener's granulomatosis, cryoglobulinemia and other systemic vasculitides are less frequent connective tissue diseases. Up to one third of patients with connective tissue disease develop a carpal tunnel syndrome , sometimes combined with a tenosinovitis. When these two conditions causing pain in the hand coexist, one of them may be missed. Connective tissue diseases are often associated with necrotising vasculitis of perineurial or endoneurial arterioles, and also with axonal damage due to secondary amyloidosis. The electromyographic findings in patients with vasculitic neuropathy show an axonal neuropathy of all fibres type, with the feature either of a symmetric polyneuropathy or asymmetric in patients with multiple mononeuropathy. A selective involvement of small fibres is rare and reflects the incidence of small fibres neuropathy in polyneuropathies in general, about 8% [26]. Pain in inflammatory neuropathy may be the heralding symptom of vasculitis anticipating sensory motor symptoms and signs. Pain is also caused by axonal injury with altered distribution of sodium channels and increased release of inflammatory mediators in nerve fibres. The expression of pro-inflammatory cytokines in peripheral nerves is increased in most vasculitic neuropathy [24] and in particular specimens from patients in whom pain is a prominent symptom [31].

ALCOHOLIC AND HIV NEUROPATHY

Alcoholic neuropathy is mainly the consequence of nutritional deficiency, particularly of thiamine and other B vitamins. It is predominantly a sensory motor axonal polyneuropathy affecting all fibres' types. Pain is at times severe; it has burning and stabbing quality, and is often associated with hyperalgesia and allodynia. A sensory ataxia often complicates coexisting cerebellar deficits. Muscle strength is relatively spared.

HIV infection causes several different types of peripheral nerve diseases, often superimposing one to the other in the same patient. At the time of death, 3 out of 4 HIV patients have a peripheral neuropathy, although clinical findings of polyneuropathy might be detected in about half to a third of the patients. In the stage of seroconversion and early stages of the HIV disease, there is high incidence of inflammatory demyelinating polyradiculoneuropathy, multiple mononeuropathy and plexopathy with clinical features akin to the same diseases affecting non-HIV subjects. In the advanced stages of the disease, the most common neuropathy is a distal axonal symmetrical mainly sensory polyneuropathy. A burning feet, with association of other painful and non-painful paraesthesiae is usually the symptomatic onset of this condition. The cause is unknown, and might include autoimmunity, nutritional deficiency, and drug toxicity. Direct viral invasion has never been proved.

DIABETIC NEUROPATHY

Diabetic neuropathy is the most common peripheral neuropathy in the western world. A recent epidemiological study reports a disorder of the peripheral nervous system in roughly 2/3 of diabetic patients [13]. A recent study has reported that pain is a significant medical issue with a moderate-to-substantial impact on quality of life in some patients with diabetic neuropathy [19]. The prevalence of painful diabetic neuropathy (PDN) in diabetic patients is ranging from 11% of an insulin treated population [6] to 25% in a hospital diabetic clinic population [10]. However, the definition of PDN does not take in account that there are several types of peripheral nerve damage in diabetic patients that can present as painful neuropathies. The most common type of peripheral neuropathy in diabetic patients is the chronic distal symmetrical polyneuropathy [63] that is often associated to positive sensory symptoms, i.e. numbness, paraesthesiae, dysesthesiae and pain. This condition represents the major source for PDN patients in clinical trials. However, several others types of painful nerve damage, with different medical history, clinical and neurophysiological examinations can be recognized in diabetic patients.

In the pure form of small fibres neuropathy associated with diabetes, pain can be the major symptom being mainly distal in the lower limbs, long lasting, burning, shooting and unremitting, often combined with allodynia and hyperalgesia, alteration of thermal perception thresholds and autonomic dysfunctions. Strength and reflexes are usually spared and sensory and motor conduction velocities and EMG remain within the normal range, generating sometimes diagnostic perplexity. The clinical picture can be divided into an acute phase, lasting a few months, followed by a long phase of progressive pain reduction associated with impairment of small fibres function with hypaesthesia to cold, warm, and painful stimuli.

In rare cases, diabetic patients may complain of an extremely severe, diffuse neuropathic pain that can disrupt completely the life of the patient. Some authors refer to this neuropathy as diabetic neuropathic cachexia [16] or acute painful diabetic neuropathy [3]. At the beginning, the painful symptoms are localized in the lower extremities, later they spread to all the lower limbs, trunk, and hands, typically worsening at night. Other clinical features include severe weight loss (up to 60% of body weight) and mood depression. The acute phase can last for a few months and then symptoms slowly subside in a time frame of 8-12 months. Treatment relays on aggressive glycemic control with insulin

infusion, which provokes weight recovery and pain reduction.

Acute nerve trunk pain is peculiar in the early phase of the painful lumbosacral radiculoplexus neuropathy [14, 15, 20], the focal and multifocal neuropathies [32, 48] and the acute painful neuropathy precipitated by strict glycemic control [8]. All these forms of diabetic neuropathies are probably due to focal nerve ischaemia, thus combining a nociceptive origin for the pain in the beginning of the history to a typical neuropathic pain that takes place later on. The painful lumbosacral radiculoplexus neuropathy is remarkable for the acute onset of a severe, often asymmetric, deep aching pain, localized proximally in the lower limb, subsequently associated with proximal weakness and wasting in the same area, without clear sensory loss. Over time, the weakness may spread distally, sometime contra laterally and sensory loss often appears together with positive sensory symptoms [14].

From the beginning of the new millennium clinical research has been focused on neuropathy related to impaired glucose tolerance (IGT). The definition of such condition is based on the result of a fasting blood glucose concentration <125 mg/dl and > 110 mg/dl or blood glucose concentration at the 2nd hours following 75 mg glucose load <199 mg/dl and > 140 mg /dl [1, 27, 52]. Recent studies describing populations of patients with idiopathic sensory neuropathy revealed that 35-50% of patients, in particular those complaining of pain, were affected by IGT [41, 55]. The damage of peripheral nerve associated with IGT is described as a painful sensory neuropathy affecting primarily small calibre afferent fibres, associated with positive and negative sensory symptoms, typically located in the lower limbs [58]. In the early stages of the disease, tendon reflexes and muscle strength are spared, as well as EMG and nerve conduction studies. On the contrary, abnormalities in the sensory examination supported by quantitative sensory testing and intraepidermal nerve fibre density reveal the diagnosis.

In the clinical setting, it is crucial to identify the nociceptive and neuropathic components to quickly and effectively treat this painful complication of diabetes that may at times reach devastating intensity.

URAEMIC NEUROPATHY

Although 80% of patients with advanced renal failure develop a sensory motor axonal polyneuropathy, with pain of moderate intensity. The most common symptoms are cramps and restlessness in the legs. Dysesthesia may be present. Unfortunately many patients with renal failure do have coexisting diabetes and the combination of these two conditions might cause an unusually severe predominantly motor polyneuropathy with intense cramps.

Concluding remarks: Not long ago neuropathic pain was rarely diagnosed, and treatment often included invasive procedure with low yield and short lasting effects such as nerve blocks. The introduction of new more effective drugs has improved the management and also contributed to a better, although still far from optimal, understanding of pain mechanisms.

In many of the described peripheral nerve diseases pain is the most distressing symptom for the patient. Often it is the cause of seeking for medical help. Pain therapists should be aware of the most common neurological presentation of peripheral neuropathic pains to guarantee timely treatment of neuropathies in which pain is the heralding symptom. Peripheral nerve experts should take advantage of the improved understanding of pain mechanisms and the new available treatments to avoid needless suffering in patients with peripheral neuropathies. The differential diagnosis between nociceptive and neuropathic components of the pain and a timely and fearless use of opioids might make the difference for controlling the most disabling pains of acute ganglionopathy and plexopathy. In the cases where nerve trunk pain opens the clinical picture, as in some diabetic neuropathies, one should start the analgesic treatment with tramadol or stronger opioids, or even steroids [14] to antagonize the nociceptive/inflammatory component of nerve injury. Many patients with small fibres neuropathy have dysautonomia with orthostatic hypotension and intestinal paresis. Preventive treatment of the side effects of analgesic drugs should be foreseen at the onset of pain therapy. Laxatives should immediately be added in case of opioid prescription in these patients and blood hypotension properly controlled with hydrofludrocortisone acetate and also head and upper body elevation while in resting position.

REFERENCES

[1] Alberti, K.G., Zimmet, P.Z. (1998) Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet. Med.*, **15**(7), 539-553.

[2] Alberts, D.S., Noel, J.K. (1995) Cisplatin-associated neurotoxicity: can it be prevented? *Anticancer Drugs*, **6**, 369-383.

[3] Archer, A.G., Watkins, P.J., Thomas, P.K., Sharma, A.K., Payan, J. (1983) The natural history of acute painful neuropathy in diabetes mellitus. *J. Neurol. Neurosurg. Psychiatry*, **46**, 491-499.

[4] Backonja, M.M. (2003) Defining neuropathic pain. *Anesth. Analg.*, **97**, 785-90.

[5] Bennett, G.J., Ochoa, J.L. (1991) Thermographic observations on rats with experimental neuropathic pain. *Pain*, **45**, 61-67.

[6] Boulton, A.J., Drury, J., Clarke, B., Ward, J.D. (1982) Continuous subcutaneous insulin infusion in the management of painful diabetic neuropathy. *Diabet. Care*, **5**(4), 386-390.

[7] Burgoon, C.F.Jr, Burgoon, J.S., Baldridge, G.D. (1957) The natural history of herpes zoster. *JAMA*, **164**, 265-269.

[8] Caravati, C.M. (1993) Insulin neuritis: a case report. *Va. Med. Mon.*, **59**, 745-746.

[9] Casey, E.B., Jellife, A.M., Le Quesne, P.M., Millett, Y.L. (1973) Vincristine neuropathy. Clinical and electrophysiological observations. *Brain*, **96**, 69-86.

[10] Chan, A.W., MacFarlane, I.A., Bowsher, D., Wells, J.C., Bessex, C., Griffiths, K. (1990) Chronic pain in patients with diabetes mellitus; comparison with a non-diabetic population. *The pain Clinic*, **3**, 147-159.

[11] Chaudhry, V., Chaudhry, M., Crawford, T.O., Simmons-O'Brien, E., Griffin, J.W. (2003) Toxic neuropathy in patients with pre-existing neuropathy. *Neurology*, **60**(2), 337-340.

[12] Dougherty, P.M., Cata, J.P., Cordella, J.V., Burton A., Weng, H.R. (2004) Taxol-induced sensory disturbance is characterized by preferential impairment of myelinated fiber function in cancer patients. *Pain*, **109**, 132-142.

[13] Dyck, P.J., Kratz, J.L., Karnes, J.L., Litchy, W.J., Klein, R., Pach, J.M., Wilson, D.M., O'Brien, P.C., Melton, L.J. 3rd, Service, F.J. (1993) The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: The Rochester Diabetic Neuropathy Study. *Neurology*, **43**, 817-824.

[14] Dyck, P.J., Norell, J.E., Dyck, P.J. (1999) Microvasculitis and ischemia in diabetic lumbosacral radiculoplexus neuropathy. *Neurology*, **10**; **53**(9), 2113-21.

[15] Dyck, P.J., Windebank, A.J. (2002) Diabetic and nondiabetic lumbosacral radiculoplexus neuropathies: new insights into pathophysiology and treatment. *Muscle Nerve,* **25**(4), 477-491.

[16] Ellenberg, M. (1974) Diabetic neuropathic cachexia. *Diabetes*, **23**, 418-423.

[17] Falk, R.H., Comenzo, R.L., Skinner, M. (1997) The systemic Amyloidosis. *N. Engl. Med. J.*, **337**, 898-909.

[18] Fields, H.L., Rowbotham, M., Baron, R. (1998) Postherpetic neuralgia: irritable nociceptors and deafferentation. *Neurobiol. Dis.*, **5**, 209-227.

[19] Galer, B.S., Gianas, A., Jensen, M.P. (2000) Painful diabetic polyneuropathy: epidemiology, pain description, and quality of life. *Diabetes Res. Clin. Pract.*, **2**, 123-128.

[20] Garland, H.T. (1955) Diabetic amyotrophy. *Br. Med. J.*, **2**, 1287-1290.

[21] George, K.K., Pourmand, R. (1997) Toxic myopathies. *Neurol. Clin.,* **15**(3), 711-730.

[22] Glynn, C., Crockford, G., Gavaghan, D. (1990) Epidemiology of shingles. *J. Roy. Soc. Med.*, **83**, 617-619.

[23] Hansson, P.T., Lacerenza, M., Marchettini, P. (2001) Aspects of clinical and experimental neuropathic pain: the clinical perspective. In: Hansson, P.T., Fields, H.L., Hill, R.G., Marchettini, P. Eds, Neuropathic pain: pathophysiology and treatment. Progress in Pain Research and Management. Seattle, IASP Press. Vol **21**, pp. 1-18.

[24] Heuss, D., Schloffer-Weigel, B., Sommer, C. (2003) Diagnosis and therapy of vasculitic neuropathy. *Fortschr. Neurol. Psychiatr*., **71**, 172-186.

[25] Hiura, A. (2000) Neuroanatomical effects of capsaicin on the primary afferent neurons. *Arch. Histol. Cytol.*, **63**(3), 199-215.

[26] Johannsen, L., Smith, T., Havsager, A.-M., Madsen, C., Kjeldsen, M.J., Dalsgaard, N.J., Gaist, D., Schrøder, H.D., Sindrup, S.H. (2001) Evaluation of patients with symptoms suggestive of chronic polyneuropathy. *J. Clin. Neuromusc. Disease,* **3**(2), 47-52.

[27] Kahn, R. (1997) Report of the Expert Committee on the diagnosis and classification of diabetes mellitus and its complications. *Diabetes Care*, **20**, 1183-1197.

[28] Kalfakis, N., Panas, M., Karadima, G., Floroskufi, P., Kokolakis, N., Vassilopoulos, D. (2002**)** Hereditary neuropathy with liability to pressure palsies emerging during vincristine treatment. *Neurology,* **59**(9), 1470-1471**.**

[29] Kaplan, J.G., Einzig, A.I., Schaumburg, H.H. (1993) Taxol causes permanent large fiber peripheral nerve dysfunction: a lesson for preventative strategies. *J. Neurooncol*., **16**, 105-107.

[30] Lindblom, U. (1985) Assessment of abnormal evoked pain in neurological pain patients and its relation to spontaneous pain: a descriptive and conceptual model with some analytical results. In: Fields, H.L., Dubner, R., Cervero, F. Eds, Proceeding of the Fourth World congress on Pain. Advances in Pain Research and Therapy. New York, Raven Press. Vol. **9**, pp. 409-423.

[31] Lindenlaub, T., Sommer, C. (2003) Cytokines in sural nerve biopsies from inflammatory and non-inflammatory neuropathies. *Acta Neuropathol.*, **105**, 593-602.

[32] Longstreth, G.F., Newcomer, A.D. (1977) Abdominal pain caused by diabetic radiculopathy. *Ann. Intern. Med*., **86**, 166-168.

[33] Lozeron, P., Nahum, L., Lacroix, C., Ropert, A., Guglielmi, J.M., Said, G. (2002) Symptomatic diabetic and non-diabetic neuropathies in a series of 100 diabetic patients. *J. Neurol.,* **249**(5), 569-575.

[34] Marchettini, P. (1993) Muscle pain: animal and human experimental and clinical studies. *Muscle Nerve*, **16**, 1033-1039.

[35] Marchettini, P., Formaglio, F., Lacerenza, M. (2001) Iatrogenic painful neuropathic complications of surgery in cancer. *Acta Anaesthesiologica Scandinavica*, **45/9**, 1090-1094.

[36] Marchettini, P., Simone, D., Caputi, G., Ochoa, J.L. (1996) Pain from excitation of identified muscle nociceptors in humans. *Brain Res.,* **740**, 109-116.

[37] Max MB. (2002) Clarifying the definition of neuropathic pain. *Pain,* **96**, 406-7.

[38] Merskey, H., Bogduk, N. (1994 reprint 2002) Classification of chronic pain: Descriptions of chronic pain syndromes and definitions of pain terms. Second Edition. Seattle, IASP Press. pp 212.

[39] Molinuevo, J.L., Graus, F., Serrano, C., Rene, R., Guerrero, A., Illa, I. (1998) Utility of anti-Hu antibodies in the diagnosis of paraneoplastic sensory neuropathy. *Ann Neurol*., **44**, 976-980.

[40] Moulin, D.E., Hagen, N., Feasby, T.E., Amireh, R., Hahn, A. (1997) Pain in Guillain-Barré syndrome. *Neurology*, **48** (2), 328-331.

[41] Novella, S.P., Inzucchi, S.E., Goldstein, J.M. (2001) The frequency of undiagnosed diabetes and impaired glucose tolerance in patients with idiopathic sensory neuropathy. *Muscle Nerve*, **24**(9), 1229-1231.

[42] Ochoa, J.L. (1970) Isoniazid neuropathy in man: quantitative electron microscope study. *Brain*, **93**(4), 831-850.

[43] Ochoa, J.L., Campero, M., Serra, J., Bostock, H. (2005) Hyperexcitable polymodal and insensitive nociceptors in painful human neuropathy. *Muscle Nerve,* **32**(4), 459-472.

[44] Ochoa, J.L., Serra, J., Campero, M. (1996) Pathophysiology of human nociceptor function. In: Belmonte, C., Cervero, F. Eds, Neurobiology of nociceptors. Oxford, Oxford University Press. pp 489-516.

[45] Ochoa, J.L., Torebjörk, E.K. (1983) Sensations evoked by intraneural microstimulation of single mechanoreceptor units innervating the human hand. *J. Physiol. (Lond.)*, **342**, 633-654.

[46] Pareyson, D. (2003) Diagnosis of hereditary neuropathies in adult patients. *J. Neurol.*, **250**(2), 148-160.

[47] Polomano, R.C., Bennett, G.J. (2001) Chemotherapy-evoked painful peripheral neuropathy. *Pain Medicine,* **2**(1), 8-14.

[48] Raff, M.C., Asbury, A.K. (1968) Ischemic mononeuropathy and mononeuropathy multiplex in diabetes mellitus. *N. Engl. J. Med.*, **279**, 17-21.

[49] Ragozzino, M.W., Melton, L.J., Kurland, L.T., Chu, C.P., Perry, H.O. (1982) Population based study of herpes zoster and its sequelae. *Medicine*, **61**, 310-316.

[50] Rowbotam, M.C., Fields, H.L. (1989) Post-herpetic neuralgia: the relation of pain complaint, sensory disturbance, and skin temperature. *Pain*, **39**(2), 129-144.

[51] Rudnicki, S.A., Dalmau, J. (2000) Paraneoplastic syndromes of the spinal cord, nerve, and muscle. *Muscle Nerve*, **23**, 1800-1818.

[52] Russel, J.W., Feldman, E.L. (2001) Impaired glucose tolerance – Does it cause neuropathy? *Muscle Nerve,* **24**(9), 1109-1112.

[53] Scadding, J.W. (1980) The permanent anatomical effects of neonatal capsaicin on somatosensory nerves. *J. Anat.,* **131** (3), 471-482.

[54] Schiffmann, R., Scott, L.J.C. (2002) Pathophysiology and assessment of neuropathic pain in Fabry disease. *Acta Paediatr*., **439**, 48-52.

[55] Singleton, J.R., Smith, A.G., Bromberg, M.B. (2001) Painful sensory polyneuropathy associated with impaired glucose tolerance. *Muscle Nerve*, **24**(9), 1225-1228.

[56] Sommer, C. (2003) Painful neuropathies. *Curr. Opin. Neurol.,* **16**, 623-628.

[57] Suarez, J.I., Cohen, M.L., Larkin, J., Kernich, C.A., Hricik, D.E., Daroff, R.B. (1997) Acute intermittent porphyria: Clinicopathologic correlation. Report of a case and review of the literature. *Neurology,* **48**(6), 1678-1683.

[58] Sumner, C.J., Sheth, S., Griffin, J.W., Cornblath, D.R., Polydefkis, M. (2003) The spectrum of neuropathy in diabetes and impaired glucose tolerance. *Neurology*, **60**(1), 108-111.

[59] Sunderland, S. (1991) Miscellaneous causes of nerve injuries. In: Sunderland, S. Ed, Nerve injuries and their repair. A critical appraisal. Edinburgh, Churchill-Livingstone Press. pp. 197-199.

[60] The Italian Guillain- Barré study group (1996) The prognosis and main prognostic indicators of Guillain- Barré syndrome: a multicenter prospective study of 297 patients. *Brain*, **119**, 2053-2061.

[61] Thomas, E., Hay, E.M., Hajeer, A., Silman, A.J. (1998) Sjögren syndrome: a community- based study of prevalence and impact. *Br. J. Rheumatol.*, **37**, 1069-1076.

[62] Verstappen, C.C., Heimans, J.J., Hoekman, K., Postma, T.J. (2003) Neurotoxic complications of chemotherapy in patients with cancer: clinical signs and optimal management. *Drugs*, **63**, 1549-1563.

[63] Watkins, P.J., Thomas, P.K. (1998) Diabetes mellitus and the nervous system. *J. Neurol. Neurosurg. Psychiat.*, **65**(5), 620-632.

[64] Woolf, C.J., Mannion, R.J. (1999) Neuropathic pain: aetiology, symptoms, mechanisms, and management. *Lancet*, **5**, 353(9168): 1959-1964.

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