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Diabetic Neuropathic Pain Pathophysiology and Pain Management.

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Abstract

Background: Diabetes Mellitus (DM) is the most common cause of neuropathy in the Western world. There are 12,000,000 patients with non-insulin dependent DM (NIDDM) in the USA and 1,000,000 patients with insulin dependent DM (IDDM). At present 20% of people more than 65 years old have DM, by 2010 it will be more than 30%. Neuropathy occurs in NIDDM and IDDM, but may develop sooner after diagnosis in NIDDM. Medication selection should be individualized, considering side effects, potent beneficial or deleterious effects on comorbidities, and whether prompt onset of pain relief is necessary.

Key words: Diabetes Mellitus, Neuropathic Pain.

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Introduction

Neuropathic pain develops as a result of lesions or disease affecting the somatosensory nervous system either in the periphery or centrally. Examples of neuropathic pain include painful polyneuropathy, postherpetic neuralgia, trigeminal neuralgia, and post-stroke pain. Clinically, neuropathic pain is characterized by spontaneous ongoing or shooting pain and evoked amplified pain responses after noxious or non-noxious stimuli. Methods such as questionnaires for screening and assessment focus on the presence and quality of neuropathic pain. Management of neuropathic pain requires an interdisciplinary approach, centred around pharmacological treatment. A better understanding of neuropathic pain and, in particular, of the translations of pathophysiological mechanisms into sensory signs will lead to a more effective and specific mechanism-based treatment approach. Others may have symptoms such as pain, tingling, or numbness—loss of feeling—in the hands, arms, feet, and legs. Nerve problems can occur in every organ system, including the digestive tract, heart, and sex organs.[1-3]

Classification of Diabetic Neuropathy

Diabetic neuropathy is heterogeneous (Thomas and Tomlinson 1993). [Table 2] shows one classification. Importantly many patients present with >1 form of neuropathy, e.g. polyneuropathyand carpal tunnel syndrome (CTS).[1]

Diagnosis

~20% of neuropathy patients remain without a etiologic diagnosis after routine lab studies including B12, folate, ANA, rheumatoid factor, ESR, immunofixation electrophoresis, RPR, TSH,CBC, and comprehensive metabolic panel. Recent reports suggest that some of these have impaired glucose tolerance (IGT) with glucose of 144-199 mg/dl in a 2 hr glucose tolerance test (Novella et al 2001, Russell and Feldman 2001, Singleton et al 2001). The more convenient test of HbA1c is insensitive. 0% of diabetics have other reasons for neuropathy; these causes must be sought.[1]

Pathogenesis

The causes are probably different for different types of diabetic neuropathy. Researchers are studying how prolonged exposure to high blood glucose causes nerve damage. Nerve damage is likely due to a combination of factors: metabolic factors, such as high blood glucose, long duration of diabetes, abnormal blood fat levels, and possibly low levels of insulin; neurovascular factors, leading to damage to the blood vessels that carry oxygen and nutrients to nerves; autoimmune factors that cause inflammation in nerves; mechanical injury to nerves, such as carpal tunnel syndrome; inherited traits that increase susceptibility to nerve disease; lifestyle factors, such as smoking or alcohol use.[3]

Treatment and primary and secondary Prevention

Control of hyperglycemia delays the appearance of neuropathy and slows progression. The Diabetes Control and Complications Trial found that intensive IDDM therapy reduced thefrequency of neuropathy by 60% over 5 years (DCCT Research Group 1993). Pancreatictransplantation appears to halt the progression of diabetic neuropathy, but does not clearly reverseexisting neuropathy (Kennedy et al 1990, Navarro et al 1997).[1]

Pain Management

Small Fiber Polyneuropathy

Pain is the main complaint, most commonly distally, described in similar terms as discussed above.Autonomic dysfunction is frequently present. On exam there is distal sensory loss affecting painand temperature, with relative preservation of the large fiber functions vibration, proprioception,reflexes and strength. NCS are normal or minimally abnormal, since such tests assess primarilylarge, fast-conducting fibers. Quantitative sensory testing (QST) is abnormal in 60% 100%.[2]

Autonomic Neuropathy

Visceral autonomic neuropathy was present in 7% of IDDM patients and 5% of NIDDM patientsin one series (Dyck et al 1993), but subclinical evidence is present in 30% after 10 years. Thevariable clinical features can be mild or incapacitating (Thomas and Tomlinson 1993) [Table 3]. Only the major manifestations are discussed here.[2]

Diabetic thoracoabdominal/truncal neuropathy/ radiculopathy

This is characterized by pain around the abdomen or lower chest described as burning, stabbing, boring, belt-like or deep aching. Cutaneous hyperesthesia and abdominal wall weakness occur.While onset is unilateral, symptoms may spread to the opposite side as well as to higher orlower dermatomes. Often patients are referred to neurologists only after cardiac and gastrointestinal disorders have been investigated.[2]

Asymmetric Lower Limb Motor Neuropathy (Diabetic Amyotrophy)

Synonyms include proximal diabetic neuropathy, diabetic polyradiculopathy, diabetic femoralneuropathy, diabetic lumbar plexopathy, and diabetic lumbosacral plexus neuropathy. Theprevalence is ~0.1%, patients are usually men above age 50 with poorly controlled NIDDM and oftenrecent weight loss. Pain is almost always at the onset, usually in the territory of lower thoracic and upper lumbar roots. This may be preceded by anorexia. Paresthesiae and hyperesthesiae are common.Weakness, generally in the upper legs, follows the pain.[1,2]

Symptoms and Types of diabetic neuropathies

Symptoms depend on the type of neuropathy and which nerves are affected. Some people with nerve damage have no symptoms at all. For others, the first symptom is often numbness, tingling, or pain in the feet. Symptoms are often minor at first, and because most nerve damage occurs over several years, mild cases may go unnoticed for a long time. Symptoms can involve the sensory, motor, and autonomic—or involuntary—nervous systems. In some people, mainly those with focal neuropathy, the onset of pain may be sudden and severe.[3]

Peripheral neuropathy

Peripheral neuropathy, also called distal symmetric neuropathy or sensorimotor neuropathy, is nerve damage in the arms and legs. Feet and legs are likely to be affected before hands and arms. Many people with diabetes have signs of neuropathy that a doctor could note but feel no symptoms themselves. Symptoms of peripheral neuropathy may include numbness or insensitivity to pain or temperature, a tingling, burning, or prickling sensation sharp pains or cramps, extreme sensitivity to touch, even light touch, loss of balance and coordination.[3]

Autonomic neuropathy

Autonomic neuropathy affects the nerves that control the heart, regulate blood pressure, and control blood glucose levels. Autonomic neuropathy also affects other internal organs, causing problems with digestion, respiratory function, urination, sexual response, and vision. In addition, the system that restores blood glucose levels to normal after a hypoglycemic episode may be affected, resulting in loss of the warning symptoms of hypoglycemia. Autonomic neuropathy affects the nerves in the heart, stomach, intestines, bladder, sex organs, sweat glands, eyes, and lungs.[3]

Neuropathy and Pain

In some diabetic patients, onset of pain is attributable to acute normalization of blood sugar at the onset of insulin therapy (insulin neuritis). While in others it coincides with dramatic weight loss. Aside from these particular conditions, it is frequently estimated that 10-20% of patients with diabetic neuropathy exhibit pain as one of the symptoms. This number may well be an underestimation.[3,4]

Pain Relief

Treatment of painful diabetic neuropathy are oral medications. People with severe nerve pain may benefit from a combination of medications or treatments and should consider talking with a health care provider about treatment options. Medications used to help relieve diabetic nerve pain include tricyclic antidepressants, such as amitriptyline, imipramine, and desipramine (Norpramin, Pertofrane; other types of antidepressants, such as duloxetine (Cymbalta), venlafaxine, bupropion (Wellbutrin), paroxetine (Paxil), and citalopram (Celexa); anticonvulsants, such as pregabalin (Lyrica), gabapentin (Gabarone, Neurontin), carbamazepine, and lamotrigine (Lamictal); opioids and opioidlike drugs, such as controlled-release oxycodone, an opioid; and tramadol (Ultram), an opioid that also acts as an antidepressant. Duloxetine and pregabalin are approved by the U.S.[3]

Antiepileptics

Gabapentin and pregabalin are effective in diabeticPPN, with dose-dependent effects for pregabalin(several negative studies for 150 mg/day, mainly positivestudies for 300–600 mg/day) and similar efficacybetween gabapentin and the TCA nortriptyline in a recent class I study. Side effects include dizziness,somnolence,peripheral oedema,

weight gain, asthenia,headache and dry mouth. In a recent comparative trial,only two side effects differentiated gabapentin andnortriptyline: dry mouth (more frequent with nortriptyline)and concentration disorders (more frequent with gabapentin).[4]

Opioids agonist

Oxycodone, tramadol and tramadol/ acetaminophencombination reduce pain in diabetic PPN.Side effects include mainly nausea and constipation,but long-term use of opioids may be associated withmisuse (2.6% in a recent 3-year registry study ofoxycodone in mainly diabetic NP, although higherrates were also reported).[4,34] Tramadol should beused with caution in elderly patients because of risk ofconfusion and is not recommended with drugs actingon serotonin reuptake such as SSRIs. The tramadol/acetaminophen combination appears better tolerated.[4]

Opioids

The Opioids analgesics have unequivocally shown effectiveness in the treatment of PDPN. Whilethese agents, specifically tramadol, oxycodone, and morphine,are recommended as second-line therapy inrecent practice guidelines, their long-term utility has yet to be elucidated. Tramadol, a unique mu-opioidagonist with serotonergic reuptake inhibition, is supportedby a large clinical database in PDPN studies.[18-20]

Methadone

A potent mu-opioid agonist, additionally possesses numerous other pharmacologic properties such as serotonin and norepinephrine reuptake inhibition, and n-methyl-d-aspartate inhibition, proposed mechanisms of central sensitization, allodynia, and neural plasticity associated with long-standing diabetes.[18-20]

Current Therapies

In the absence of an established pathogenic mechanism for either neuropathy or pain, there is no prophylactic therapy against painful diabetic neuropathy. Only duloxetine (Cymbalta) and pregabalin (Lyrica) currently have FDA-approved labeling for treating painful diabetic neuropathy.

Antidepressants

While antidepressants maybe classified in a variety of ways, we will use the classifications of selective serotonin reuptake inhibitors(SSRI), serotonin-norepinephrine reuptake inhibitors(SNRI), tricyclic antidepressants (TCA), and atypicalantidepressants (those which do not conveniently fall within one of these groups).[11-15]

Anticonvulsants

The anticonvulsants have more recently become considered first-line for the treatment of PDPN, largely due to a reduced side effect profile compared to antidepressants and the generic availability of gabapentin. Anticonvulsants, as a class, typically possess more drug interactions, with the exceptionof the gabapentinoids (pregabalin and gabapentin), compared to their antidepressant counterparts.[17-20]

Zonisamide

Should not be used in patients with adocumented sulfa medication allergy while topiramateis not prone to this sensitivity. Oxcarbazepine, a derivative of carbamazepine,exhibits similar sodium channel blockade with areduced incidence of severe hepatotoxicity and blooddyscrasias. The risk of a Steven Johnson Syndrome rash still exists, as well as hyponatremia. No serumdrug monitoring is required and the medication isusually well-tolerated when titrated quickly.[20]

Antipsychotics

The introduction of the “atypical” antipsychotics, socalled because of their diverse pharmacology separatefrom that of pure dopaminergic blockade, resulted in the investigation of these agents for the treatment ofpain of a neurogenic origin. Numerous atypical antipsychoticshave been studied for chronic noncancer painsyndromes, although few have focused on PDPN.[18-20]

Anesthetics/ anti-arrhythmic

The anesthetic anti-arrhythmics are perhaps the mostunder-utilized of the potential strategies for alleviationof neuropathic pain associated with diabetes,although careful monitoring by experienced practitionersis paramount.. Lidocaine, mexilitine, and tocainide have all shown benefit for PDPN in smaller, RCTs. Some painclinicians recommend the administration of a lidocaine infusion to assess the potential response to oral mexilitine, a lidocaine congener. Others report success with periodic lidocaine infusions without transition to an oral alternative.[18-20]

Vasodilators

As the numerous pathophysiologic theories for PDPN. Emerged over the past two decades, several treatments, such as direct vasodilators, were investigated for analgesia in this pain syndrome. Isosorbide dinitrate spray is recommendedas a second-line therapy option for PDPN based on the AAN evidenced based guidelines.[19-20]

Conclusion

Diabetic neuropathies are nerve disorders caused by many of the abnormalities common to diabetes, such as high blood glucose. Treatment first involves bringing blood glucose levels within the normal range. Good blood glucose control may help prevent or delay the onset of further problems. Foot care is an important part of treatment. Treatment also includes pain relief and other medications as needed, depending on the type of nerve damage.

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