Natural history of diabetic neuropathy biology essay

Science, Biology

The epidemiology and natural history of DN remain poorly defined, in part because of variable criteria for the diagnosis, failure of many physicians to recognize and diagnose the disease and lack of standardized methodologies used for the evaluation of these patients{}]. [63] It has nonetheless been estimated that 50% of patients with diabetes have DN and 2. 7 million have painful neuropathy in the United States. DN is grossly under diagnosed and under treated. The natural history of neuropathies separates them into two very distinctive entities, namely those which progress gradually with increasing duration of diabetes, and those which remit, usually completely. Sensory and autonomic neuropathies generally progress, while mononeuropathies, radiculopathies, and acute painful neuropathies, although symptoms are severe, are short-lived and tend to recover]. Progression of DN is related to glycemic control in both type 1 and type 2 diabetes]. It appears that the most rapid deterioration of nerve function occurs soon after the onset of type1 diabetes and within 2-3 years there is a slowing of the progress with a shallower slope to the curve of dysfunction. In contrast, in type 2 diabetes, slowing of nerve conduction velocities (NCVs) may be one of the earliest neuropathic abnormalities and often is present even at diagnosis.[98] {}{}] After diagnosis, slowing of NCV generally progresses at a steady rate of approximately 1 m/sec/year, and the level of impairment is positively correlated with duration of diabetes. Although most studies have documented that symptomatic patients are more likely to have slower NCVs than patients without symptoms, these do not relate to the severity of symptoms. In a long term follow up study of type 2 diabetes patients [99]], electro physiologic abnormalities in the lower limb increased

from 8% at baseline to 42% after 10 years, with a decrease in sensory and motor amplitudes, indicating axonal destruction, was more pronounced than the slowing of the NCVs. Using objective measures of sensory function such as the vibration perception threshold test, the rate of decline in function has been reported as 1-2 vibration units/year. However, there now appears to be a decline in this rate of evolution. It appears that host factors pertaining to general health and nerve nutrition are changing. This is particularly important when doing studies on treatment of DN, which have always relied on differences between drug treatment and placebo and have apparently been successful because of the decline in placebo-treated patients]. Recent studies have pointed out the changing natural history of DN with the advent of therapeutic lifestyle change, and the use of statins and ACE inhibitors, which have slowed the progression of DN and drastically changed the requirements for placebo-controlled studies. [100] It is also important to recognize that DN is a disorder wherein the prevailing abnormality is loss of axons that electro physiologically translates to a reduction in amplitudes and not conduction velocities, and changes in NCV may not be an appropriate means of monitoring progress or deterioration of nerve function. Small, unmyelinated nerve fibers are affected early in DM and are not reflected in NCV studies. Other methods, that do not depend on conduction velocities, such as quantitative sensory testing, autonomic function testing or skin biopsy with quantification of intra epidermal nerve fibers (IENF), are necessary to identify these patients.[101-103]]ReflexesClinicalNerve Conduction Abnormalities

Onset of Clinical Disease

Subclinical

Signs

Vibratory SensationPressure Sensation (Monofilament)

Time

Symptoms (numbness, pricking, pain)Fig 6: Diabetic Peripheral Neuropathy Can Progress Over Time. [104]

Clinical Presentation of Diabetic Neuropathy

History

In type 1 diabetes mellitus, distal polyneuropathy typically becomes symptomatic after many years of chronic prolonged hyperglycemia. Conversely, in type 2, it may present after only a few years of known poor glycemic control. Patients with type 2 diabetes mellitus may sometimes already have neuropathy at the time of diagnosis. [89, 99]Since diabetic neuropathy can manifest with a wide variety of sensory, motor, and autonomic symptoms, a structured list of symptoms can be used to help screen all diabetic patients for possible neuropathy. Sensory symptoms may be negative or positive, diffuse or focal. Negative sensory symptoms include feelings of numbness or deadness, which patients may describe as being akin to wearing gloves or socks. Loss of balance, especially with the eyes closed, and painless injuries due to loss of sensation are common. Positive symptoms may be described as burning, prickling pain, tingling, electric shock-like feelings, aching, tightness, or hypersensitivity to touch. Motor

problems may include distal, proximal, or more focal weakness. In the upper extremities, distal motor symptoms may include impaired fine hand coordination and difficulty with tasks such as opening jars or turning keys. Foot slapping and toe scuffing or frequent tripping may be early symptoms of foot weakness. Symptoms of proximal limb weakness include difficulty climbing up and down stairs, difficulty getting up from a seated or supine position, falls due to the knees giving way, and difficulty raising the arms above the shoulders. In the most common presentation of diabetic neuropathy with symmetrical sensori motor symptoms, minor weakness of the toes and feet may be seen, but severe weakness is uncommon and should prompt investigation into other causes, such as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), or vasculitis. More severe weakness may be observed in asymmetrical diabetic neuropathy syndromes. Autonomic symptoms may be sudomotor (dry skin due to lack of sweating or excessive sweating in defined areas), pupillary (poor dark adaptation, sensitivity to bright lights), cardiovascular (postural lightheadedness, fainting), urinary (urgency, incontinence, dribbling), gastrointestinal (diarrhea, constipation, nausea, or vomiting), and sexual (erectile impotence and ejaculatory failure in men, loss of ability to reach sexual climax in women). A generally accepted classification of diabetic neuropathies divides them broadly into symmetric and asymmetric neuropathies. Development of symptoms depends on many risk factors, such as total hyperglycemic exposure, elevated lipids, blood pressure, smoking, increased height, and high exposure to other potentially neurotoxic agents such as ethanol. Genetic factors may also play a role. [105]Establishing the diagnosis

requires careful evaluation since patients with diabetes may have neuropathy from another cause. Depending on the physician practices studied, this group may represent 10-26% of diabetic patients with neuropathy.[106]Symmetrical polyneuropathies involve multiple nerves diffusely and symmetrically. Distal symmetrical sensorimotor polyneuropathyMost common manifestation of diabetic neuropathy. The syndrome has been defined in many ways, but a few key criteria are commonly accepted: The patient must have diabetes mellitus by one of the widely accepted definitions such as those outlined by the American Diabetes Association or World Health Organization.[94]The severity of polyneuropathy should be commensurate with the duration and severity of the diabetes. Other causes of sensorimotor polyneuropathy have been excluded. Sensory, motor, and autonomic functions affected in varying degrees, with sensory abnormalities predominatingChronic symmetrical symptoms affecting peripheral nerves in a length-dependent pattern (the longest nerves affected first). Commonly presents as painful paresthesias and numbness, which begin in the toes and ascend proximally in a stocking-like distribution over months and yearsWhen sensory symptoms ascend above the knees, hands develop similar symptoms, progressing proximally in a glove-like distributionAnterior aspect of the trunk and vertex of the head may be affected at a very late stageMild weakness of foot muscles and decreased ankle and knee reflexes occur commonlyLoss of sensation predisposes to development of foot ulcers and gangrene[107]With impaired proprioception and vibratory perception, gait may be affected (sensory ataxia)Small-fiber neuropathyDistal symmetrical neuropathy involving predominantly small-

diameter sensory fibers (A delta and C fibers)Manifests as painful paresthesias that patients perceive as burning, stabbing, crushing, aching, or cramp like, with increased severity at nightLoss of pain and temperature sensation with relative sparing of distal reflexes and proprioceptionDiabetic autonomic neuropathyPure autonomic is neuropathy rare. Some degree of autonomic involvement is present in most patients with distal symmetrical diabetic polyneuropathy, but patients may not notice autonomic problems. Signs may include orthostatic hypotension, resting tachycardia, loss of sinus arrhythmia, anhydrosis, bowel or bladder dysfunction, and small pupils sluggishly reactive to light. Diabetic neuropathic cachexiaPrecipitous and profound weight loss followed by severe and unremitting cutaneous pain, small-fiber neuropathy, and autonomic dysfunctionOccurs more often in older men; impotence is common. Muscle weakness is uncommon. Symptoms usually improve with prolonged glycemia control. Symptoms are often refractory to other pharmacologic treatment. Limited anecdotal improvement is reported with non pharmacologic treatments such as sympathectomy, spinal cord blockade, and electrical spinal cord stimulation. Recovery may be incomplete and prolonged over many months. Asymmetric neuropathies include single or multiple cranial or somatic mononeuropathies. Syndromes include median neuropathy of the wrist (carpal tunnel syndrome), or other single or multiple limb mononeuropathies, thoracic radiculoneuropathy, lumbosacral radiculoplexus neuropathy, and cervical radiculoplexus neuropathy. These syndromes are distinguished from typical distal diabetic polyneuropathy by the following characteristics: (1) they often have a monophasic course, (2) some are associated with inflammatory

angitis and ischemia (eg, lumbosacral radiculoplexus neuropathy) and may appear acutely or subacutely, and (3) they have a weaker association with total hyperglycemic exposure than symmetrical polyneuropathies. Cranial mononeuropathyCranial nerves (CN) III, IV, VI, VII, and II are most often involved. CN III, IV, and VI disease manifests as acute or sub acute periorbital pain or headache followed by diplopia. Muscle weakness is typically in the distribution of a single nerve, and pupillary light reflexes are usually spared. Complete spontaneous recovery usually occurs within 3 months. Facial neuropathy manifests as acute or sub acute facial weakness (taste is not normally involved) and can be recurrent or bilateral. Most recover spontaneously in 3-6 months. Anterior ischemic optic neuropathy manifests as acute visual loss or visual field defects (usually inferior altitudinal). The optic disk appears pale and swollen; flame-shaped hemorrhages may be present. Somatic mono neuropathiesFocal neuropathies in the extremities caused by entrapment or compression at common pressure points or by ischemia and subsequent infarction. Entrapment and compression tend to occur in the same nerves and at the same sites as in individuals without diabetes. Median nerve entrapment at the wrist (carpal tunnel syndrome) is more common in patients with diabetes and can be treated in the same manner as in patients without diabetes. Symptoms are often bilateral. The susceptibility to ulnar nerve entrapment at the elbow or common peroneal nerve entrapment at the fibular head is not definitely increased among patients with diabetes. Neuropathy secondary to nerve infarction presents acutely, usually with focal pain associated with weakness and variable sensory loss in the distribution of the affected nerve. Multiple nerves may be

affected (mono neuritis multiplex). Diabetic thoracic radiculoneuropathyBurning, stabbing, boring, belt-like, or deep aching pain usually begins unilaterally; then may become bilateral. Skin hypersensitivity and allodynia (pain with normally innocuous touch) may occur. Numbness in a dermatomal distribution, most prominent in distal distribution of inter costal nerves. Single or multiple spinal roots are involved. Contiguous territorial extension of symptoms may occur in a cephalac, caudal, or contralateral direction. In the trunk, thoraco abdominal neuropathy or radiculopathy may cause chest and/or abdominal pain in the distribution of thoracic and/or upper lumbar roots. Weakness presents in the distribution of the affected nerve root, e. g., bulging of the abdominal wall from abdominal muscle paresis (thoracic root). Patients older than 50 years are affected most often; it is more common in diabetes mellitus type 2 and is often associated with significant weight loss. Coexisting diabetic distal symmetrical polyneuropathy often is present. Diabetic radiculoplexus neuropathyThe syndrome may occur in the cervical or lumbosacral distributions and is referred to in the literature by various designations including diabetic amyotrophy, Bruns-Garland syndrome, and diabetic plexopathy, among others. The most frequent initial symptom is sudden, severe, unilateral pain in the hip/ lower back or shoulder/ neck. Weakness then develops days to weeks later. Atrophy of the limb musculature may occur. Allodynia, paresthesias, and sensory loss are common. Symptoms usually begin unilaterally and may later spread to the opposite side. Reflexes in the affected limb may be depressed or absent. This condition often occurs in patients older than 50 years with poorly controlled diabetes. It is more

common in men than in women. Significant weight loss occurs in 50% of patients. The course is generally monophasic with improvement over many months; however, some residual deficits often remain.

Physical Signs

The first clinical sign that usually develops in diabetic symmetrical sensorimotor polyneuropathy is decrease or loss of vibratory and pinprick sensation over the toes. As disease progresses, the level of decreased sensation may move upward into the legs and then into the hands and arms, a pattern often referred to as " stocking and glove" sensory loss. Very severely affected patients may lose sensation in a " shield" distribution on the chest. Deep tendon reflexes are commonly hypoactive or absent and weakness of small foot muscles may develop. More focal findings may be seen with injury to specific nerves or groups of nerves, as described above. Blood pressure measurements in patients with autonomic neuropathy may show orthostatic hypotension with reduced compensatory tachycardia.

Differential Diagnosis of Diabetic Neuropathy

Alcohol (Ethanol) related neuropathyChronic Inflammatory Demyelinating PolyradiculoneuropathyNutritional neuropathySarcoidosis and neuropathyToxic neuropathyVasculitis neuropathyThyroid disease related neuropathyAmyloid PolyneuropathySpinal Cord TumorsVitamin B 12 deficiency

Cranial mononeuropathy

Intracranial aneurysmsBell palsy

Thoracoabdominal neuropathy

Herpes zosterSpinal tumorsMyocardial infarctionAcute cholecystitisAcute appendicitisDiverticulitis

Lumbosacral radiculoplexopathy

Anterior disk protrusionSpinal cord tumorsMalignant nerve root infiltrationsInflammatory neuropathies