Diabetic Neuropathy

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No one involved in the planning of this CME activity had any relevant financial relationships to disclose. Authors/faculty have nothing to disclose

Chair: *Mark A. Ferrante, MD*

Objectives

Objectives - Participants will acquire skills to (1) discuss the clinical characteristics and risk factors of treatment-induced diabetic neuropathy and review diabetic autonomic neuropathies, (2) examine whether peripheral neuropathy occurs in association with glucose impairment and review the clinical characteristics and outcomes of diabetic sensorimotor peripheral neuropathy, (3) explain which mononeuropathies occur more frequently in diabetic patients and discuss the clinical features and potential treatments of these mononeuropathies, and (4) examine the diabetic neuropathies that are due to inflammatory and immune causes, review their clinical and pathological findings, review results of controlled immunotherapy trials in diabetic lumbosacral radiculoplexus neuropathy, and see if an association exists between diabetes mellitus and CIDP.

Target Audience:

- Neurologists, physical medicine and rehabilitation and other physicians interested in neuromuscular and electrodiagnostic medicine
- Health care professionals involved in the management of patients with neuromuscular diseases
- Researchers who are actively involved in the neuromuscular and/or electrodiagnostic research

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Diabetic Neuropathy

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Autonomic and Treatment-Induced Diabetic Neuropathy

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PREVALENCE OF DIABETIC AUTONOMIC NEUROPATHY

Symptoms of autonomic dysfunction secondary to diabetes have been reported in detail over the past century. However, the relative frequency of autonomic dysfunction reported in diabetes has been difficult to establish in individuals or populations because of the variable involvement of the different organ systems. As an example, some degree of erectile dysfunction is seen in more than 50% of males with diabetes while cardiovascular autonomic neuropathy is seen in 15-30%, but this depends on the population studied, the type of test used for diagnosis, and the duration of diabetes. If all tests of autonomic function are considered in the diagnosis of diabetic autonomic neuropathy, prevalence rates as high as 90% have been reported.[1-4] Therefore, understanding the frequency of autonomic neuropathy in a given population requires a description of the type of end organ function measured and the specific methodology used to define an abnormal result.

There is an association between sensory neuropathy and autonomic neuropathy that is also variably reported depending on the methods of evaluation. Thus, if autonomic neuropathy is defined by orthostatic hypotension and presence of sensory neuropathy is defined by abnormal nerve conduction studies the relative frequency of abnormality may be lower than 5%. However, if skin biopsy measurements of nerve fiber density are defined for small fiber neuropathy and cardiovagal abnormalities are used to define autonomic neuropathy, rates higher than 30% may be expected in a general population of patients with diabetes. Although autonomic neuropathy is frequently seen in patients with a distal length-dependent sensory or sensorimotor neuropathy some patients may present with autonomic neuropathy in isolation.[4]

MANIFESTATIONS OF DIABETIC AUTONOMIC NEUROPATHY

Pupillary

Sympathetic innervation of the iris shows earlier and more extensive dysfunction than parasympathetic innervation, resulting in an inability to rapidly or completely dilate the pupil in darkness. Patients often describe difficulty seeing and driving at night. This finding may be seen at the time of diabetes diagnosis and is related to glycemic control.[5,6]

Gastrointestinal

Gastroparesis is one of the more common, and most feared, complications of diabetes. Seen in 30-50% of individuals with longstanding diabetes, it results in early satiety, nausea, vomiting, inconsistent medication absorption, and weight loss, and it is often described in association with "brittle diabetes."[7-9] Gastric emptying is measured through use of scintigraphy of technetium labeled egg whites 4 hours after eating. In addition to delayed gastric emptying, esophageal dysmotility is commonly seen in diabetes (approximately 50% of individuals with diabetes > 10 years) and may mimic cardiac pain in some patients. Lower gastrointestinal dysfunction in diabetes may present as either constipation or diarrhea. The constipation is typically not as severe as other autonomic failure syndromes. However, diabetic diarrhea can be disabling, with frequent bowel movements that are often nocturnal, resulting in dehydration, sleep disruption, and significant anxiety.[8]

Genitourinary

Erectile dysfunction is the most prominent manifestation of diabetic autonomic neuropathy in males, and it may manifest as decreased tumescence, rigidity and rarely retrograde ejaculation.[8,10] In women, dyspareunia may be the presenting symptom of diabetic autonomic neuropathy due to dry, atrophic vaginal walls.[8,10] Bladder dysfunction can present in both genders as a consequence of autonomic neuropathy. Efferent autonomic bladder dysfunction may present with decreased voiding sensation and decreased frequency which may increase risks of urinary tract infections (UTIs). Afferent autonomic neuropathy often occurs after longer diabetes duration and results in increasing post-void residuals and increased UTIs.[11]

Sudomotor

Sweating abnormalities are common in diabetes and may be the most prevalent manifestation of a distal neuropathy.[12] In early cases of neuropathy, distal hyperhidrosis may occur transiently which eventually develops into a length-dependent anhidrosis.[13] The development of dry, cracked skin can increase the risk for skin breakdown and is a portal to infection. As the region of anhidrosis grows larger, central hyperhidrosis occurs to maintain thermoregulatory capacity. However, the primary complaint by patients is often increased central and facial perspiration.[14]

Cardiovascular

One of the initial findings of a cardiovascular autonomic neuropathy in diabetes is a resting tachycardia.[4,15] Associated symptoms include exercise intolerance and orthostatic intolerance. There is some evidence that cardiovascular autonomic neuropathy may also result in impaired left ventricular function in individuals without underlying cardiac disease.[4,16-19] In addition, there is an association between cardiovascular autonomic neuropathy and painless myocardial ischemia. As autonomic neuropathy worsens, orthostatic hypotension (defined as a sustained fall in systolic blood pressure > 20 mgHg or fall in diastolic blood pressure > 10 mmHg within 3 minutes of standing) is more prevalent and more severe.[8,19,20]

Hypoglycemic Unawareness

Hypoglycemic unawareness is also referred to as an autonomic neuropathy of the adrenal medulla or hypoglycemia associated autonomic failure.[21] Hypoglycemia is a complex physiologic stress that activates the hypothalamic-pituitary axis and the sympatho-adrenal system.[22] Hypoglycemia results in increased circulating glucocorticoids and catecholamines, but also results in blunted counter-regulatory autonomic responses to subsequent hypoglycemia thus reducing the defense against falling blood glucose and creating a vicious cycle of repeated episodes of hypoglycemia in insulin-treated diabetes.[21]

NATURAL HISTORY OF DIABETIC AUTONOMIC NEUROPATHY

Natural history studies traditionally have investigated the involvement of a single organ system in diabetes, such as cardiovascular autonomic neuropathy, thus true rates of disease progression are relatively unknown. In patients with newly diagnosed type 2 diabetes, a 10-year natural history study based in Kuopio, Finland, investigated the rates of cardiac autonomic neuropathy progression using a combination of orthostatic blood pressure tests, Valsalva maneuvers, and heart rate response to deep breathing. The rate of parasympathetic dysfunction increased from 5% to 65% over 10 years in individuals with diabetes, compared to control subjects who increased from 2% to 28%.[23] Sympathetic dysfunction in individuals with diabetes increased from 7% to 24% compared to control subjects who increased from 6% to 9%.[23] In subjects with type 1 diabetes, data have been gleaned from the Epidemiology of Diabetes Interventions and Complications (EDIC) and Diabetes Control and Complications Trial (DCCT) trials where heart rate variability, Valsalva maneuvers, and postural blood pressures were repeated 13-14 years after enrollment in the DCCT trial. Cardiovascular autonomic neuropathy (defined as abnormal results of any autonomic test) increased from 3-5% at baseline to 29-35% (intensive versus conventional treatments, accordingly).[24] Disease progression in type 1 and type 2 diabetes has been linked to glycemic control, age, duration of diabetes, hypertension, and hyperlipidemia.[1,4,24-26] Similarly detailed studies on autonomic dysfunction in the gastrointestinal, genitourinary, respiratory, sudomotor, or pupillary systems have not been conducted.

TESTS OF AUTONOMIC FUNCTION IN DIABETES

Diagnosis of autonomic neuropathy in diabetes can be accomplished through relatively simple bedside measurements in the most advanced cases, but typically requires detailed autonomic testing in the majority of patients. Specific tests commonly performed by neuromuscular specialists are reviewed below, but additional tests of autonomic function can be performed such as urodynamic studies, gastrointestinal transit studies, anorectal manometry, and pupillometry.

Tests of Cardiovascular Autonomic Physiology

Tests of cardiovascular function measure both the sympathetic and parasympathetic divisions of the autonomic nervous system simultaneously. Standard tests of parasympathetic function include the heart rate response to deep breathing, a Valsalva maneuver, and standing. Standard tests of sympathetic adrenergic function include the blood pressure response to a Valsalva maneuver, standing or tilt table testing.

Heart Rate Response to Respiration

The heart rate response to deep, paced breathing provides a simple and effective measurement of the cardiovagal parasympathetic nervous system. Respiration produces a sinus arrhythmia that is mediated by the vagus nerve. The amplitude of the variation in heart rate is a quantitative measure of parasympathetic health, with reduced variance seen with increasing age and disease severity, but with a number of known confounding factors such as medication use. Testing is performed with the patient in the recumbent position. Ideally, respiratory bands surrounding the abdomen and chest should be used to provide a noninvasive record

of adequate respiratory effort. Continuous electrocardiogram monitoring is used to evaluate heart rate response. The patient is asked to take deep inspirations lasting 5 s, followed by expiration lasting 5 s. A total of 6-8 breathing cycles are recorded and the five largest consecutive cycles are measured, averaged, and the heart rate range (maximum-minimum) is determined. In diabetic autonomic neuropathy, decreased heart rate variability is seen compared to age- and gender-matched healthy subjects.

Heart Rate and Blood Pressure Response to a Valsalva Maneuver

The Valsalva maneuver is performed by blowing into a tube against 40 mmHg of resistance for approximately 15 s. The Valsalva maneuver is separated into four distinct phases. Phase I begins with the onset of straining with a transient increase in blood pressure secondary to increased intrathoracic pressure and mechanical compression of the great vessels. Phase II is separated into two parts: early and late. In early phase II, decreased venous return secondary to mechanical compression of the great vessels results in decreased stroke volume, cardiac output, and blood pressure. After a few seconds late phase 2 begins: the falling blood pressure is sensed by the carotid baroreceptors resulting in sympathetically-mediated vasoconstriction and parasympathetic withdrawal leading to increased peripheral vascular resistance and an increase in cardiac output due to increased heart rate. Phase III occurs when subjects stop exhaling against resistance. Blood pressure transiently decreases due to increased capacitance of the great vessels. Phase IV occurs as the heart rate decreases and the blood pressure returns to normal or above, deemed the "overshoot." The blood pressure overshoot is a consequence of increasing venous return, stroke volume, and cardiac output into a vasoconstricted circulation. The heart rate and beat-to-beat blood pressure responses to the Valsalva maneuver are required for interpretation of the results. In diabetic autonomic neuropathy, decreased heart rate variability is seen compared to age- and gender-matched healthy subjects with a greater fall in phase II blood pressure and diminished phase IV blood pressure overshoot.

Heart Rate and Blood Pressure Response to Standing and Tilt Testing

The initial response to standing involves a shift in blood volume of 300-800 mL from the central to the peripheral vascular system leading to an abrupt increase in the heart rate mediated by inhibition of vagal tone. There is a gradual increase in heart rate for another 12 s that is most likely a baroreflex mediated response to a fall in blood pressure due to release of vasoconstrictor tone. A new baseline heart rate is reached within 30 s, and the ratio of tachycardia at 15 s to bradycardia at 30 s is a measure of parasympathetic function. The 30:15 ratio is not usually measured during tilt testing because the table transition to an upright position is typically too slow to provoke a full heart rate response. The blood pressure response to both upright tilt and stand is monitored, and orthostatic hypotension can be detected in individuals with diabetic autonomic neuropathy. Prolonged tilt table testing can detect delayed orthostatic hypotension in some individuals, where blood pressure falls may occur after prolonged periods of standing.[27]

Tests of Sudomotor Physiology

Thermoregulatory sweating is unique to humans and primates and is mediated through eccrine sweat glands. Sweating is a sympathetically-mediated response derived from the hypothalamus through preganglionic cholinergic neurons that synapse in the paravertebral ganglia with postganglionic sympathetic cholinergic sudomotor axons. Tests of sudomotor function aid in localizing and monitoring disease progression in diabetic autonomic neuropathy. Traditional neurophysiologic measurements of sudomotor function include thermoregulatory sweat testing (TST), quantitative sudomotor axon reflex testing, silicone impressions and sympathetic skin response (SSR), and the recent addition of quantitative direct and indirect axon reflex testing.[28,29] TST stimulates sweating by raising the core body temperature and using an indicator dye to identify regions of anhidrosis, thus measuring both pre- and postganglionic sudomotor function. The SSR measures electrodermal activity and provides a surrogate measure of sympathetic cholinergic sudomotor function but does not actually measure sweat output and has a very high degree of variability, thereby limiting its clinical utility. All other tests of sudomotor function measure the postganglionic sudomotor axon reflex by measuring sweat output after iontophoresis of a cholinergic agent (such as acetylcholine). In diabetes, a distal loss of sudomotor function is commonly seen in patients with a length-dependent neuropathy, and it may be the earliest method to detect a distal small fiber neuropathy.[12]

IMPLICATIONS OF AUTONOMIC NEUROPATHY IN DIABETES

Pupillary

Individuals with pupillary dysfunction may be relatively asymptomatic, but they can have impaired night vision and need to be aware that nocturnal driving may become unsafe. In addition, evidence of pupillary autonomic dysfunction has been associated with increased microalbuminuria and retinopathy 12 years later, suggesting an increased risk of general microvascular disease in these individuals.[6]

Gastrointestinal

The implications for autonomic neuropathy of the gastrointestinal tract are frequently subclinical, but when more pronounced can have a major impact on medical management of disease and lifestyle. Delayed esophageal transit can result in heart burn, dysphagia, and chest pain. Delayed gastric emptying is associated with nausea, vomiting, and weight loss. As gastroparesis worsens, food and medication absorption are delayed thereby worsening glucose control. Patients on insulin are at risk for hypoglycemia because of difficulty regulating the timing of injections. There are also inconsistent medication responses due to variable absorption which may have profound changes on treatment efficacy and compliance. When gastroparesis is more severe, urgent hospitalization may be required for intractable vomiting and electrolyte disturbances. In the small and large bowels, bacterial overgrowth and diarrhea may result in pain, diarrhea, and pseudo-obstruction.

Genitourinary

The medical consequences of genitourinary dysfunction primary concern the increased risks of UTI in the setting of incomplete bladder emptying. Individuals with diabetes experience both more frequent and more severe UTIs than nondiabetic patients and are predisposed to more complex complications such as pyelonephritis. However, the sexual dysfunction experienced by both genders is even more common, can have a major impact on quality of life, and is an increasingly frequent topic of discussion at clinical visits.[1]

Sudomotor

Distal sudomotor dysfunction can lead to dry, cracked skin and a portal to infection in at-risk patients. Aggressive application of topical moisturizers is the only effective way to reduce the associated cutaneous complications in dry environments. More diffuse anhidrosis can result in proximal hyperhidrosis and may become a source of social embarrassment. In patients with more widespread anhidrosis, the ability to thermoregulate in warm environments can become compromised and limit ability to perform certain occupations and may restrict activities of daily living, resulting in relocation to cooler climates in extreme cases.

Cardiovascular

Cardiovascular autonomic neuropathy can manifest as exercise intolerance in patients with diabetes. The reduced heart rate and blood pressure response to exercise can limit cardiac output and place patients and risk if they seek to exercise using their heart rate as a guideline. Patients at risk for cardiovascular autonomic neuropathy should have an exercise stress test prior to participating in an exercise program.[4] Diabetic patients with cardiac autonomic neuropathy have two to three times higher levels of morbidity and mortality during perioperative periods than nondiabetic patients. Both the surgeon and anesthesiologist need to be aware of the patient's autonomic neuropathy status prior to anesthesia because of risks of arrhythmias and exaggerated blood pressure swings during surgery.

Orthostatic hypotension, although infrequently severe, may be associated with supine hypertension. Orthostatic hypotension may require specialized management to raise diurnal blood pressures (to avoid syncope and injury) while avoiding nocturnal supine hypertension and increased risks of renal dysfunction.

Overall, patients with diabetic cardiovascular autonomic neuropathy have an increased mortality risk of two to three times that of diabetic individuals without cardiovascular autonomic neuropathy. The risk increases with the severity of the autonomic neuropathy.[4]

Hypoglycemic Unawareness

Patients that experience hypoglycemia have an attenuated catecholamine and glucocorticoid response to falling blood glucose. This, in turn, results in a greater risk of additional, and more profound, hypoglycemia in the future. Overall, patients with hypoglycemic unawareness have a greater than 25 fold increased risk of severe hypoglycemia than patients with an intact catecholamine and glucocorticoid response. Intentional relaxation of glycemic control is often required in these cases, although there are a number of barriers to compliance because of psychological reliance on glycemic control to prevent disease progression among individuals with longstanding diabetes.

TREATMENT-INDUCED DIABETIC NEUROPATHY

Treatment-induced diabetic neuropathy is a rare painful neuropathy associated with rapid changes in glycemic control. It was first reported by Caravati in 1933 when he encountered a diabetic women that developed numbness, tingling, and shooting pains in the lower extremities that appeared 4 weeks after the initiation of insulin treatment.[30] The disorder has also been described as diabetic neuropathic cachexia and acute painful diabetic neuropathy.[31-33] The neuropathy appears to be more common in individuals with type 1 diabetes, but is also seen in those with type 2 diabetes. Treatment-induced neuropathy is associated with rapid glycemic control using insulin, oral hypoglycemic medications, and, in rare cases, by severe dietary restriction.[31,32,34-36] In the author's cohort of patients, many individuals had glycosylated hemoglobin A1C scores in the 12-20% range for many years until they elected to voluntarily control their glucose. The A1C typically fell to the 6-9% range within 3 months or less. Symptoms of neuropathic pain usually began within a few weeks of the improved glucose control as shown in the Figure.

The most common clinical presentation includes severe burning and shooting pains in a length-dependent or generalized pattern within weeks of the onset of glucose control. The pain reflects the characteristic diurnal variation of neuropathy, but is still severe throughout the day. The pain is usually continuous and often accompanied by allodynia and hyperalgesia. The reported pain is typically more severe and more refractory to treatment that typical cases of painful diabetic neuropathy. Most patients require a number of different pharmacologic agents simultaneously for pain control, including narcotics, and still report inadequate relief. The neuropathic pain may gradually begin to spontaneously improve 12-24 months after the onset of glycemic control.

On neurologic examination, there is often a loss of thermal and pain sensation while large fiber modalities, motor function, and deep tendon reflexes are relatively unaffected. Nerve conduction studies are typically normal in these individuals. Structural examination of small nociceptive C fibers by skin biopsy shows distal or diffuse loss of unmyelinated intraepidermal nerve fibers with numerous morphologic changes noted within a few weeks of the onset of neuropathic pain. The distribution of pain roughly correlates with the regions of intraepidermal nerve fiber density (IENFD) loss. Neurologic examination findings may begin to improve slightly in some individuals 18-24 months after the onset of glycemic control. On skin biopsy, there may also be an associated increase in IENFD approximately 12-24 months after the onset of glycemic control.

Although autonomic symptoms are present in the majority of individuals with treatment-induced neuropathy, they are often overshadowed by the neuropathic pain and frequently not reported unless they interfere with activities of daily living.

Typical symptoms include postural dizziness and lightheadedness, nausea, diarrhea, and erectile dysfunction. Less frequent findings include gastroparesis and syncope.[34] Autonomic testing may show mild-to-moderate sympathetic and parasympathetic dysfunction within a few weeks of the onset of pain. The exact timing of the autonomic dysfunction in relation to glycemic control has not been fully elucidated. The data suggest widespread damage to the small unmyelinated and lightly myelinated nerve fibers that is temporally related to the rapid improvement in glucose control. There is a correlation between the rapidity and degree of glycemic change and the severity of autonomic and neuropathic symptoms and signs.[34]

Treatment-induced neuropathy appears to be a diffuse microvascular disease that can affect other organ systems. In the author's studies of patients with this disorder, rapidly progressive retinopathy was seen in all subjects after the onset of glycemic control, whether or not there was a prior history of retinopathy. This phenomenon has been noted within the DCCT and a number of other studies and is referred to as early worsening retinopathy.[37-39] In addition, a significant worsening of renal function in the majority of subjects with treatment induced diabetic neuropathy has been detected. The cause of the early worsening of retinopathy and nephropathy is not known. A number of cytokines and trophic factors including the vascular endothelial growth factor, insulin growth factor, interleukin-6, interleukin-8, and tumor necrosis factor-α have been implicated in the pathogenesis of early worsening retinopathy.[39,40] It is hypothesized that upregulation of these cytokines and trophic factors in the setting of intensive glycemic control is responsible for the rapidly progressive retinopathy.[39,40]

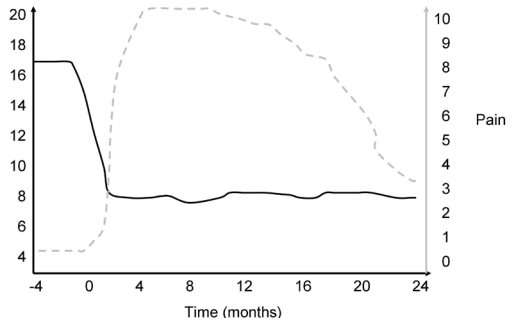

Figure. Treatment induced diabetic neuropathy.
The left Y axis demonstrates the hemoglobin A1C value, which corresponds to the black solid line on the graph. The right Y axis reflects the pain scores (0 = no pain, 10 = maximal pain), which correspond to the grey dashed line on the graph. The X axis is the time in months. During the period of time prior to rapid glycemic control (−4 to 0 months on the X axis) subjects have minimal neuropathic pain. After a rapid drop in hemoglobin A1C scores, there is a rapid rise in pain that is typically sustained for 12-24 months.

After 18 months of glucose control with glycosylated hemoglobin A1C values in the 6-8.[5] range, many patients with treatment-induced neuropathy had improvement to pain, symptoms and signs of autonomic dysfunction, neurologic examination findings, and intraepidermal nerve fiber density. There were greater improvements seen in those individuals with type 1 diabetes, although the reasons for this have not been established. Individuals with type 1 diabetes were younger, had less comorbid medical conditions, such as hyperlipidemia and hypertension, and ultimately had lower glycosylated hemoglobin A1C values than individuals with type 2 diabetes. All of these potential variables may have contributed to the differences in outcomes between the two groups with treatment-induced neuropathy. Nonetheless, there were still improvements in neuropathic pain in all patients after a prolonged period of glucose control which still portends a better outcome than other forms of diabetic neuropathy.

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Diabetic Polyneuropathies: Classification, Epidemiology, Mechanisms & Treatment

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INTRODUCTION

This discussion will report on epidemiology, mechanisms, and treatment of polyneuropathies associated with diabetes mellitus (DM). Some general facts are understood regarding diabetic polyneuropathies (DPNs):

- Diabetic polyneuropathies are a family of various types of neuropathy.
- There is no type of polyneuropathy occurring only in DM—their designation as "diabetic" is based on their increased prevalence in DM.
- Many neuropathies occurring in patients with DM are not diabetic neuropathies but are due to another cause—examination and further testing may be needed to properly diagnose these neuropathies. This should be a special challenge for neuromuscular physicians.
- Many, perhaps most, cases of generalized DPN are asymptomatic (subclinical).
- Although generalized DPN may be preventable (at least to an extent) by control of cardiovascular factors and hyperglycemia, no preventative pharmaceutical medication (other than glucose lowering drugs) has been approved by regulatory agencies in the United States.
- There are Federal Drug Administration approved medications to modulate pain and ameliorate autonomic symptoms.
- There is a major public health effort to deal with the healthcare burden of being overweight, having an unhealthy diet, and lacking physical fitness, all considered major causes of type 2 DM.
- Screening of foot sensation is being tested to prevent the high morbidity and cost of plantar ulcers and neurogenic arthropathy.
- Prospective trials of impaired glycemia (impaired fasting plasma glucose, impaired glucose tolerance, and impaired A1C), although indicative of prediabetes, do not appear to be directly associated with a higher prevalence of DPN.

CLASSIFICATION

The presently accepted classification of diabetic polyneuropathies is shown here.[4]

Focal and Multifocal Varieties

- Mononeuropathies (e.g., cranial nerve III, IV, and VI neuropathies, median neuropathy at the wrist [carpal tunnel syndrome {CTS}], ulnar neuropathy at the elbow, and fibular neuropathy at the knee)
- Radiculoplexus neuropathies
  - Cervical
  - Thoracic
  - Lumbosacral (Bruns-Garland syndrome, femoral neuropathy, multiple mononeuropathy, and many other names)
  - Combinations of the above (multiple monoradiculoplexus neuropathies)

Generalized Neuropathies

- Typical (diabetic sensorimotor polyneuropathy [DSPN])
- Atypical polyneuropathy (e.g., intercurrent small fiber sensory and autonomic polyneuropathy)

None of these varieties of neuropathy are found only in DM. The case that DM itself is involved in pathogenesis therefore depends mainly on their increased prevalence in DM.[2,3]

DIABETIC POLYNEUROPATHY

Typical DPN or DSPN is a length-dependent sensorimotor polyneuropathy which usually develops on a long standing history of chronic hyperglycemia induced by DM (either type 1 or 2). Its diagnosis is strengthened by the simultaneous occurrence of diabetic retinopathy or nephropathy. The staging approach, agreed to by the Toronto Diabetic Neuropathy Expert Group investigators, is shown here:

N0: No abnormality of nerve conduction, e.g., Σ 5 nerve conduction normal deviates > 2.5th percentile
N1a: Nerve conduction abnormality without "unequivocally abnormal" neuropathic signs or symptoms
N1b: Nerve conduction abnormality and "unequivocally abnormal" neuropathic signs
N2a: Nerve conduction abnormality ± signs and neuropathic symptoms, lesser severity than stage 2b
N2b: Nerve conduction abnormality, ankle dorsiflexion weakness ≥ 50%, and neuropathic symptoms less than N3
N3: As described in textbook *Diabetic Neuropathy.*[5]

Atypical diabetic polyneuropathies are intercurrent small fiber sensory or autonomic polyneuropathies.[1] The evidence that chronic hyperglycemia is a major cause is weak. Some authors suggest that altered immunity may be involved.

Epidemiology

The prevalence of varieties of DPN (as outlined in the classification listed above) has not been adequately studied. In Figure 1, the prevalence of typical polyneuropathy (DSPN) in the Rochester Diabetic Neuropathy Study (RDNS) cohort is shown. In prevalence studies, typical DPN (DSPN) occurred in 47.3%. Electrophysiologic evidence of median neuropathy at the wrist (carpal tunnel syndrome) occurred in 32.3%.

Mechanism

Historically, three broad categories of mechanisms of DSPN deserve attention.

- An early view was that atherosclerosis was the likely cause of DSPN. Undoubtedly, peripheral vascular disease due to atherosclerosis can cause ischemic damage of nerves but this does not explain the usual onset and progression of DSPN. If atherosclerosis is involved in generalized polyneuropathy, it presumably occurs only in very severe peripheral arterial disease.
- Microvessel disease with early degeneration of pericyte cells and with basement membrane reduplication (Figure 2) needs to be considered but even here metabolic alterations need to be considered as well.
- It is now widely accepted that metabolic derangements secondary to chronic hyperglycemia are implicated in the development of DSPN. There are many, perhaps more than 100, metabolic alterations attributable to chronic hyperglycemia. These include myo-inositol deficiency, accumulation of tissue polyols (e.g., fructose and sorbitol), protein kinase C beta 1 activity, accumulation of advanced glycation endproducts, oxidative stress, and other metabolic derangements. Recent studies have focused on metabolic derangements at the mitochondrial level. While treatments to prevent or inhibit development of these metabolic derangements have shown promise in animal models, none has achieved acceptance by U.S. regulatory agencies.

Unequivocally, however, studies have shown that prevention of chronic hyperglycemia prevents development of DSPN at least to a degree.

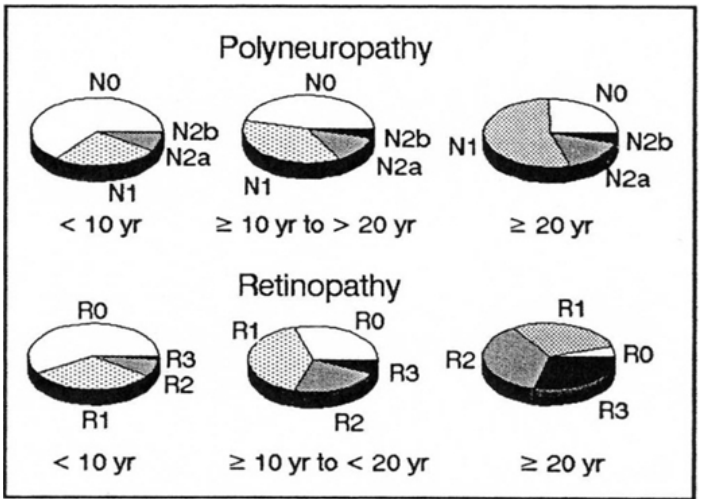

Figure 1. The change in the stage distribution of neuropathy (top) and retinopathy (bottom) with increasing duration of diabetes mellitus. From Dyck, Kratz, Karnes, et al.[3]

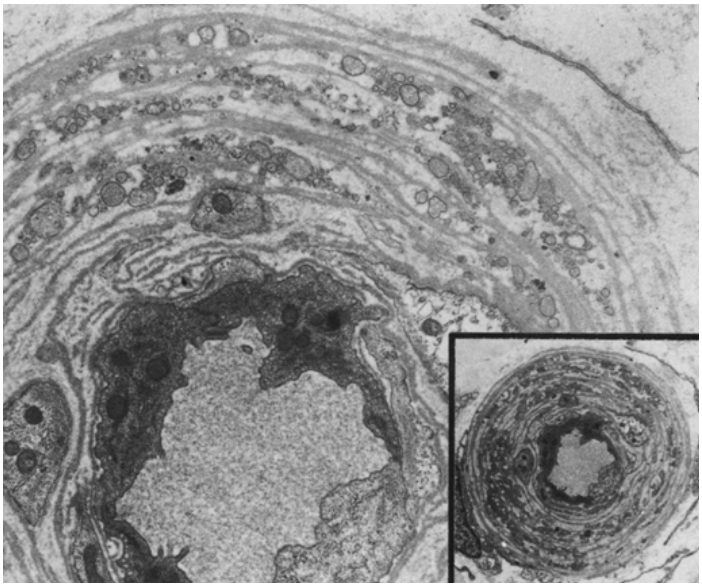

Figure 2. This microvessel shows severe basement membrane reduplication and a very high number of cellular debris among the basement membrane leaflets. Basement membrane leaflets are often incomplete and fragmented. (magnification = 14K × before 25% reduction; inset, magnification = 3.6K × before 25% reduction.). From Giannini and Dyck.[6]

Treatment

- Prevention of type 2 DM may be possible at least to a degree by prevention of obesity, avoiding unhealthy diets, and adequate physical activity.
- DSPN appears to be preventable, at least to a degree, by rigorous control of hyperglycemia and vascular risk factors.
- Pain and autonomic symptoms are treatable.
- Screening of foot sensation (if done well) may be used to prevent foot complications.

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Mononeuropathies in Diabetics

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INTRODUCTION

The questions to be addressed in this discussion include:

- Is the prevalence of limb mononeuropathies higher in diabetics than in nondiabetics?
- Are these located at the common compression/entrapment sites or elsewhere?
- If there is an increase in mononeuropathies in diabetics, why is this so?
- Does the management of mononeuropathies in diabetics differ than those in nondiabetics?

PREVALENCE

Diabetic polyneuropathy (DPN) is the most frequent peripheral nerve complication of diabetes mellitus (DM). The issue as to whether there is a higher prevalence of some mononeuropathies in diabetics has been discussed for decades. Many neuromuscular specialists and practitioners of electrodiagnostic (EDX) testing have observed that there is such a relationship, at least for some of the common mononeuropathies. Almost all of the literature prior to 2000 is flawed and generally inconclusive (for a detailed review see Wilbourn[1]). There are now contemporary data to support this relationship, and most current classifications of diabetic neuropathies include mononeuropathies.

SITES

The mononeuropathies for which there is evidence for a raised prevalence in diabetics are carpal tunnel syndrome (CTS), ulnar neuropathy at the elbow (UNE), common peroneal (fibular) neuropathy (CPN), and meralgia paresthetica (MP). Other nerves at other sites will be mentioned briefly. Two other diabetic neuropathy syndromes that are the result of multifocal damage to roots, plexuses, and individual peripheral nerves are excluded because they are not mononeuropathies. One is diabetic lumbosacral radiculoplexus neuropathy (DLRPN) (also known as diabetic amyotrophy, diabetic lumbosacral plexopathy, diabetic polyradiculopathy, proximal diabetic neuropathy, and Bruns-Garland syndrome). The other is acute brachial plexus neuropathy.

MECHANISMS

Polyneuropathy Lends Susceptibility to External Compression

Individual nerves appear to be more sensitive to acute or chronic external pressure if the patient or experimental animal has a polyneuropathy. The best evidence for this comes from guinea pig experiments. Plantar neuropathies in these animals develop in animals in cages with wire mesh flooring. These mononeuropathies develop more quickly in those with experimentally-induced diphtheritic polyneuropathy and are prevented if the animals are kept off their feet.[2] Similarly, rats kept in cages with wire mesh or sawdust flooring develop distal tibial neuropathies; this is accelerated in rats made diabetic with streptozotocin.[3] Disordered axonal transport mechanisms and microvascular and metabolic abnormalities have been suggested as underlying mechanisms for increased susceptibility to pressure.

Other Factors

Another theory focuses on the tissues and structures surrounding individual peripheral nerves. "Repetitive injury, inflammation, thickening or stiffness of overlying ligaments, tethering of the nerve proximal and distal to the site of compression . . . might . . . all be involved in [the] pathogenesis of focal entrapment/compression neuropathies in diabetics."[4] In CTS limited joint mobility is a common problem in type 1 diabetics, and its presence correlates highly with CTS.[5]

Other risk factors may combine with DM to play a role. Obesity is one such factor that predisposes to CTS and meralgia paresthetica, and there is an increased prevalence of obesity in diabetics.

Nerve infarction is another possible mechanism, but this appears to be rare. When a mononeuropathy develops acutely in a diabetic, in the absence of trauma, this may be the cause.

SPECIFIC NERVES AND MANAGEMENT

Carpal Tunnel Syndrome

Carpal Tunnel Syndrome in Nondiabetics

Several studies have investigated the epidemiology of CTS in nondiabetics, a common and apparently straightforward condition in the general population, and rates vary by study location and the methodology used.[6-10] The criteria for diagnosis vary considerably. That there is no accepted gold standard test for CTS compounds the uncertainty. Some studies base the diagnosis on symptoms only, others add a physical examination, and others use electrophysiologic criteria. In each of these approaches there are important questions regarding the sensitivity and specificity of the items being used or measured. These issues notwithstanding, the prevalence of CTS in a general population, and the impact of diagnostic criteria used, can be assessed from the study of Atroshi and colleagues.[7] Clinically and electrophysiologically confirmed CTS was found to have a prevalence of 2.7% (95% CI, 2.1-3.4%). CTS is three times as common in women as in men, and usually occurs in the 40-60 year age group. There is a further peak incidence in the 70s, when the gender ratio is more equal. There are many factors contributing to the development of CTS. Is DM one of them?

Carpal Tunnel Syndrome in Diabetics

It is widely thought that CTS is common in DM patients. The contradictory data in the literature up to 1999 have been excellently summarized by Wilbourn[1] as follows. In determining the number of patients with CTS who have coexisting diabetes, 20 studies report figures from 2.6% to 20%. Looking at the issue the other way round, that is, the number of diabetics that have CTS, eight studies revealed a range from 1% to 21%. The weight of the evidence from these earlier studies thus points to a considerably higher prevalence of CTS in diabetics compared with nondiabetics.

More recent papers support this conclusion.[11] In the Fremantle Diabetes Study of 1,284 type 2 diabetics, CTS decompression surgery was 4.2 times more frequent in diabetics than in the general population ($p<0.001$).[12] Another study of patients undergoing CTS surgery showed similar results.[13] Singh and colleagues14 showed that the lifetime risk for developing CTS in type 1 diabetics is very high, and it is related to age and DM duration but not to microvascular complications (retinopathy). Gulliford and colleagues[15] evaluated a large cohort of patients from general practices in the United Kingdom and made the interesting observation that there is an increased incidence of CTS in the 10-year period *before* the diagnosis of DM is made, i.e., in the prediabetic period. (It is generally considered that the onset of type 2 DM occurs at least 4-7 years before the diagnosis of DM.[16]) Further, in a case-controlled study of 117 patients with idiopathic moderate-to-severe CTS, a 2-hour glucose tolerance test and insulin resistance measurements showed a remarkably high number of CTS patients with impaired glucose tolerance or diabetes (even when the fasting glucose and glycosylated hemoglobin values were normal).[17] Only one recent study did not find an association between CTS and DM, but this study lacks a case control group.[18]

There are methodological problems with many of these studies, although the more recent ones are fairly robust. The criteria for the diagnosis of CTS vary—by history, examination, EDX studies, or combinations of these. The skill set of the examiner(s) is important, e.g., neuromuscular specialist or other peripheral nerve specialist versus diabetologist, internist, or family physician. The severity of the CTS and the criteria on which the grading is based are often not explicit.

Another complicating factor in assessing and interpreting these studies is that the risk of developing CTS is clearly multifactorial. One such factor is body mass index (BMI), a risk factor for both DM and CTS.

In summary, the weight of the evidence strongly supports the concept that the prevalence of CTS is higher in diabetics than nondiabetics. This is of considerable clinical importance. The precise reasons why CTS is more common in diabetics than nondiabetics are discussed above.

TESTING "IDIOPATHIC" CARPAL TUNNEL SYNDROME PATIENTS FOR DIABETES MELLITUS?

Studies have shown that the yield from routine tests for DM (fasting blood sugar) in patients with CTS is low and is therefore discouraged.[19,20] For a screening test to be cost effective it has to detect diseases that are not clinically suspected at a time when therapeutic intervention confers benefits; this has yet to be proven regarding CTS.[21] However, when more rigorous tests are used (see above) the yield of impaired glucose tolerance/mild diabetes is considerable. Making this diagnosis is important so that the patients can introduce conservative measures to reduce their risk of DM and its complications.

CLINICAL, DIAGNOSTIC, AND ELECTRODIAGNOSTIC STUDY APPROACHES TO CARPAL TUNNEL SYNDROME IN DIABETICS

Clinical

There are three important points to emphasize in the clinical approach to CTS in diabetics:

- When a diabetic reports more neuropathic symptoms in the hands than feet, or more in one hand than the other, suspect bilateral or unilateral CTS. Similarly, if the clinical deficits are worse in the hands than feet, then suspect one or more focal upper limb neuropathies.
- Examine the patient very carefully for evidence of more median than ulnar motor and/or sensory dysfunction. If these are equal, the diagnosis could be either coexistent median and ulnar neuropathies, or diabetic polyneuropathy.
- Remember that in all patients with CTS the Tinel and Phalen tests are useless because of lack of sensitivity and specificity.[22]

Electrodiagnostic Studies

Guidelines regarding the best EDX studies have been published in a report from the American Association of Electrodiagnostic Medicine, American Academy of Neurology, and the American Academy of Physical Medicine and Rehabilitation.[23] These studies are designed to localize the median nerve dysfunction to the carpal tunnel, evaluate its severity, and exclude other neurologic diagnoses.

The basic principles in each EDX study should be to compare the median and ulnar distal motor latencies and amplitudes, and those of the median, ulnar, and radial sensory nerve action potentials (SNAPs). If the symptoms are unilateral, the median conductions can be compared one hand to the other. A recent article has addressed such comparisons in diabetics with CTS and polyneuropathy.[24] The most useful measures they describe for diagnosing the former were a comparison of median palm-digit and wrist-palm sensory conduction times, and median-ulnar SNAP latency differences from stimulation of the ring finger.
Another additional technique is to compare needle electromyographic (EMG) findings in median and ulnar intrinsic hand muscles. For example, the presence of fibrillations/positive sharp waves in the former but not the latter would support the diagnosis of CTS.

When the patient has coexistent median and ulnar neuropathies, with or without some degree of polyneuropathy, the presence of a radial SNAP when the other two are absent is a useful finding. In the case of severe DPN it may not be possible to demonstrate coexisting CTS. Note also that EDX studies reveal the electrophysiological abnormalities of CTS in a significantly higher number of asymptomatic diabetics than in nondiabetics.

Ultrasound

Ultrasound has emerged as a powerful imaging technique for diagnosing focal neuropathies, particularly CTS. It may be a useful test to perform in the diabetic patient when the EDX studies are unclear, although to the author's knowledge there is no study evaluating its role in CTS in diabetics compared with nondiabetics.

MANAGEMENT OF CARPAL TUNNEL SYNDROME IN DIABETICS

When the diabetic patient has CTS that is *asymptomatic* but discovered when performing EDX studies for DPN, no specific treatment should be instituted and the patient followed. For patients with mild CTS the standard conservative measures—avoidance of excessive hand use, wrist braces worn at night—should be used, although their efficacy has not been studied in diabetics. Corticosteroid injection into the carpal tunnel is, like splinting, a venerable treatment for CTS and, along with splinting, is the principal alternative to surgery. Its role in diabetics with CTS has not been studied, to the author's knowledge.

The role of surgical decompression has been extensively studied in diabetics with CTS. Even when a generalized polyneuropathy is present, as long as it is clear that the patient also has CTS, the results of decompression are good.[25-29] Particularly impressive are the triad of articles by Thomsen and colleagues.[30-32] These evaluate in a prospective study that included a control group, the clinical, health-related quality of life and EDX recovery of diabetic CTS patients who underwent surgical decompression. Their improvement in all of these spheres was equal to the nondiabetic control group. They make the important point that marked impairment on EDX studies or signs of DPN do *not* preclude significant recovery in the diabetic patients.

In summary, there is clearly an increased prevalence of CTS in diabetics. These patients do well with surgical decompression so it is important to recognize and treat such patients in order to preserve optimum hand function.

ULNAR NEUROPATHY AT THE ELBOW

There are many diverse causes of UNEs, but they are probably more frequent in diabetics than nondiabetics. In four older and flawed studies, UNEs were found in 1-5% (mean 2%) of patients with DM.[1] Looking at the issue the other way round, there are six older series of patients with UNEs evaluated for DM.[1] Coexisting DM was present in 4-17.4% (mean 9%). In the most robust of these studies of 414 patients with UNE, 11% had DM.[33] Another useful finding is from a community based study in which the prevalence of UNE in diabetic patients is about 2%.[34] A review of a huge number of patients with UNEs evaluated in an EDX laboratory has reported that 6% had DM.[35] In a large surgical case-control study only 1.4% of the cohort studied had DM (these were then excluded from the study).[36] A case control study of risk factors for UNE did not identify DM as a definite risk factor.[37]

There is a single article that reports four type 1 diabetic patients with UNEs in the forearm.[38]

Clinical

Ulnar neuropathies in diabetics are often severe, predominantly motor, have predominantly axonal damage, are usually found in longstanding diabetics with systemic complications, and men are more affected than women.[39] Perhaps the presence of a sensory polyneuropathy obscures the usual warning paresthesias of a developing ulnar neuropathy. In the author's experience, many of these patients are surprised to be told of their UNE because sensory symptoms were absent and muscle weakness and wasting so insidious that it went unnoticed. Diabetic patients with UNEs quite often have CTS. In one series of diabetics with UNEs, 25% were of sudden onset, suggesting nerve infarction.[39]

Electrodiagnostic Studies

Standard EDX studies for UNE should be performed.[40] Ulnar SNAPs should be compared with the median and particularly radial SNAPs, but when there is significant polyneuropathy all these SNAPs may be absent. Motor conduction studies looking for abnormalities localized to the elbow are often unhelpful because the damage is predominantly axonal. Unless the patient has a coexisting CTS, needle EMG studies comparing the ulnar and median intrinsic hand muscles can be useful.

Management

Management of diabetics with UNEs has not been systematically studied. The standard conservative measures of avoiding elbow leaning and prolonged flexion during sleep should be instituted. This may help some patients with milder UNEs. For the more severe UNEs, surgery can be considered. Although not specifically studied, the results are often disappointing.[1] In terms of the specific surgical procedure, there is no data for diabetics. For other patients with idiopathic UNE, simple decompression is quicker and has fewer complications than other procedures, and so it would be a reasonable choice for the diabetic patient, if surgery is to be done at all.

In summary, there probably is an increased prevalence of UNEs in diabetics. Such UNEs are often severe with predominant axonal damage, and they do not usually respond well to surgery.

COMMON PERONEAL (FIBULAR) NEUROPATHY

The older and flawed papers referred to above, and reviewed by Wilbourn,[1] indicate that CPNs have a higher prevalence in diabetics. Better data come from a series of 116 patients with CPNs carefully evaluated clinically and electrophysiologically: 8% had DM.[41] Thus, patients with diabetes seem to be predisposed to developing CPN.

The most common cause of CPN in general is probably external compression, particularly habitual leg crossing. Emaciated diabetics may be at particular risks for such damage. The same may hold true for diabetics undergoing bariatric surgery and major weight loss.

Clinical

There are many causes of footdrop, the characteristic feature of CPN.[22,42] Careful history and physical examination go a long way to differentiate these.

Investigations

Electrodiagnostic studies should focus on whether the patient has footdrop due to CPN at the usual site at the proximal fibula, or due to diabetic polyneuropathy (in which the foot dorsiflexor muscles often are more involved than the plantar flexors), a partial sciatic neuropathy, plexopathy, or radiculopathy. If it is a CPN it may have nothing to do with diabetes and in patients with progressive symptoms the knee and peroneal nerve should be evaluated with ultrasound, computerized tomography, or magnetic resonance imaging for mass lesions that may be damaging the nerve.

Management

No specific management strategies have been evaluated for diabetics with CPN. The initial management should be to advise against external compression and habitual leg crossing, and the patient followed. If the mononeuropathy worsens, then imaging should be performed and abnormalities found may require surgery. If no cause is found in such a patient then surgical exploration should be considered because the patient may have a small lesion that has not been detected on imaging studies, or they may have nerve entrapment in the fibular tunnel. A footdrop orthosis is a useful but oft forgotten aid when weakness is marked.

MERALGIA PARESTHETICA

Meralgia paresthetica is a common focal neuropathy is due to a lesion of the lateral cutaneous nerve of the thigh of which there are many causes, However, in most patients there is no identifiable cause—"idiopathic MP."[22] A popular notion is that these patients have an anomalous course of the nerve that predisposes it to entrapment or otherwise harmless external compression, or may be entrapped in fascia, but evidence to support these mechanisms is lacking.[22]

Diabetes mellitus is often quoted as being a cause of MP. The older and flawed studies of mononeuropathies in diabetics referred to above do not support this association.[43,44] A case control study of MP in general practice did not find an increase in MP in diabetics.[45] An EDX laboratory based study of 131 cases of MP in 120 patients also showed DM not be a risk factor.[46] However, a recent population-based case control study of 262 patients with MP shows clearly that DM is a significant risk factor.[47] Patients with MP were twice as likely to have DM than the control subjects. Also, a group of diabetics followed for 10 years developed MP 7.5 times more frequently than in the general population. Further, 20% of nondiabetic patients with MP went on to develop DM over the 10-year study period. *Diabetes is thus clearly a risk factor for MP.*

Obesity has long been thought to be a predisposing factor for MP. A retrospective case-control study showed that 27% of 104 patients with MP had a higher than normal BMI, and the authors concluded that obesity doubles the risk of this disorder.[48] This has been further confirmed.[47] Age is an additional risk factor.[47] However, the association with DM is independent of obesity and age. An increase in MP is predicted as these these three risk factors increase in many populations.[47]

Clinical

The characteristic history and examination are often enough to establish the diagnosis.

Investigations

Nerve conduction studies have been described (see, for example, Seror[46]). Atypical patients may require needle EMG and imaging studies to investigate for possible lumbar radiculopathy or plexopathy. *Because of the strong correlation between MP and DM, when a patient not known for DM presents with MP, it is important to test that patient for DM.*[47]

Management

In most patients with MP the condition resolves spontaneously. In those few with painful progressive or intractable symptoms, surgical decompression or sectioning of the nerve is usually effective. The efficacy of weight loss is unknown. Whether the presence of DM has implications in terms of prognosis and management is unknown.

FEMORAL NERVE

The most common cause of femoral neuropathies is often said to be DM,[49,50] but this rarely causes a pure femoral neuropathy.[51] The femoral nerve usually bears the brunt of the damage in DLRPN (see above) so this disorder has been frequently mislabeled femoral neuropathy.[52] These comments also apply to nondiabetic lumbosacral radiculoplexus neuropathy.

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Diabetic Inflammatory Neuropathies: The Radiculoplexus Neuropathies of Diabetes Mellitus

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INTRODUCTION

Many different types of peripheral neuropathy arising from different underlying mechanisms occur in association with diabetes mellitus (DM), the most common type being a symmetrical, length-dependent, sensorimotor polyneuropathy (DPN). However, it is not DPN but some of the other types of peripheral neuropathy associated with DM that cause the most severe morbidity. One method of classifying the subtypes of diabetic neuropathy is dividing them into those that usually are symmetrical and those that usually are asymmetrical. The asymmetrical forms often are the result of compression or inflammatory causes. The largest categories of inflammatory asymmetrical diabetic neuropathy are the diabetic radiculoplexus neuropathies (DRPNs).

The DRPNs are differentiated from DPN by their acute-to-subacute symptom onset, frequent association with pain, asymmetrical pattern of involvement, and the anatomical distribution of involvement. It should be noted that similar clinical neuropathies do occur in nondiabetic patients, but an indepth review of the nondiabetic forms is beyond the scope of this discussion.

The DRPNs are frequently further separated into three anatomical subcategories of lumbosacral, thoracic, and cervical radiculoplexus neuropathies. It is important to recognize that although a distinction among the subtypes is easily made, all three types appear to be due to a common underlying pathophysiological mechanism (ischemic injury from inflammatory mechanisms) and often occur together and concurrently in the same patient.

The first, and likely the most common variety, diabetic lumbosacral radiculoplexus neuropathy (DLRPN), is the most well-known of the three entities and is a painful, rapidly evolving, asymmetric, lower-limb, paralytic neuropathy often associated with weight loss.[16] The natural history and underlying pathophysiological mechanisms of DLRPN have been long debated with many different names applied to them reflecting the multiple views that exist: diabetic myelopathy,[23] diabetic amyotrophy,[22] diabetic mononeuritis multiplex,[39] proximal diabetic neuropathy,[3] diabetic lumbosacral plexopathy,[7] diabetic polyradiculopathy,[5] Bruns-Garland syndrome,[4] and multifocal diabetic neuropathy.[42] The author's institution uses the term DLRPN as it emphasizes the multiple sites of pathological involvement (roots, plexus, and peripheral nerves) and the association of this syndrome with DM.

The second type of DRPN is diabetic thoracic radiculopathy also called truncal radiculopathy[30,45] and here called diabetic thoracic radiculoneuropathy (DTRN). The third anatomical type is diabetic cervical radiculoplexus neuropathy (DCRPN).[15,27,36] This latter type represents a form that many know as an inflammatory brachial plexopathy or neuralgic amyotrophy both clinically and electrophysiologically. The association with DM has been less well-established for the upper limb variety. Both DTRN and DCRPN may occur in patients who also have DLRPN.

DIABETIC LUMBOSACRAL RADICULOPLEXUS NEUROPATHY

As previously mentioned, a patient with one variant of DRPN often will go on to develop one of the other types. Some of these patients may eventually suffer from or even present with cranial

involvement (i.e., third nerve palsy). Given the understanding that DRPNs are due to a common underlying mechanism (usually ischemic injury from microvasculitis), much of this discussion will focus on the most clearly defined group of DRPNs, the lower limb DLRPN.

Typically, DLRPN develops in middle age or later in life in patients with type 2 DM. Its onset is often heralded by weight loss which can be quite significant (median 30 lb in the author's series).[15] At times the neurological symptoms begin suddenly, to the point that some patients recall the particular day and time the symptoms began, quite in contrast to DPN which is usually insidious in onset (Table). These sudden onset forms usually begin with pain. In other cases, the onset is not quite as dramatic but it still usually will begin in a subacute fashion. Pain is a prominent initial feature in most cases, often quickly followed by weakness and paresthesias. The pain is usually quite severe and can be of many types, including sharp or lancinating pain, hurting or deep aching pain, burning pain, and contact allodynia (pain with normal touch). Although the syndrome usually begins with asymmetrical pain and weakness (commonly beginning unilaterally and focally), it often spreads to the initially unaffected nerve segments and to the contralateral side. The clinical and pathological findings in 33 prospectively evaluated patients with DLRPN were reviewed. The syndrome was initially unilateral in 29 of 33 patients, but became bilateral in all except for one patient by the time the patients presented to the author's institution.[15] Although DLRPN has often been thought of as a motor neuropathy, it rarely is pure motor. Autonomic symptoms are very common as well. The majority of patients had alteration of sexual function, sweating abnormalities, disorder of blood pressure regulation, and other autonomic disturbances. Sensory disturbances are also common. Quantitative sensory testing in these patients typically demonstrates panmodal abnormalities (both small and large fiber involvement).

The anatomical distribution of disease is also different than DPN in which it usually almost exclusively affects the distal lower limbs. In the patients with typical, painful DLPRN, there was involvement of both proximal and distal nerve segments. It often would begin focally proximally (such as thigh weakness) or distally (such as foot drop) but then proceed to have both proximal and distal involvement and then involve the contralateral lower limb. Over time, the syndrome becomes widespread but usually stays somewhat asymmetrical and is not a length-dependent neuropathy. In fact, the notable proximal involvement is why some authors called this condition proximal diabetic (motor) neuropathy.[3,41] This terminology is not favored by the author as there is clear distal (as well as proximal) involvement and marked sensory and autonomic findings in addition to motor manifestations. Nerve conduction studies (NCSs) and needle electromyography (EMG) usually supports the concept that these are axonal radiculoplexus neuropathies with widespread but patchy neurogenic changes and prominent denervation involving lumbosacral greater than thoracic or cervical segments. In DLRPN, needle EMG often can be interpreted as showing changes of a length-dependent peripheral neuropathy with multiple superimposed lumbosacral radiculopathies. While this interpretation is not incorrect, it implies that there are two separate pathological processes occurring. This is unlikely to be two separate processes. Rather, there is a radiculoplexus neuropathy (roots, plexus, and nerve) involvement by a multifocal axonal disorder.

Although pain is prominent in typical DLRPN, in all types of DLRPN it appears that it is the weakness that is the most disabling symptom and often prompts the patient to seek clinical evaluation and it is the weakness that is often the more longterm and debilitating characteristic of the syndrome. The weakness can be quite profound; over one-half of DLRPN patients in the author's cohort who were initially ambulatory were wheelchair dependent at some point during their illness.[15] Although this syndrome is

Table. Clinical and laboratory characteristics of diabetic lumbosacral radiculoplexus neuropathy

	N	Median	Range			SD
Clinical						
Age, year	33	65.4	35.8	-	75.9	10.4
Body mass index, kg/m^2	29	25.7	17.8	-	36.7	4.9
Weight change, lb	33	-30.0	-120.0	-	0.0	32.6
Duration of neuropathy at evaluation, mo	33	6.7	1.4	-	42.0	8.9
Time to bilateral, mo	32	3.0	0.0	-	60.0	10.6
Time to maximum disability, mo	31	5.0	0.3	-	20.0	4.7
NIS total	33	43.0	7.0	-	87.0	18.6
Laboratory						
Fasting plasma glucose, mg/dL	30	144.5	75.0	-	225.0	44.3
Glycated hemoglobin, %	30	7.5	5.1	-	12.9	2.0
Creatinine, mg/dL	30	0.9	0.7	-	3.4	0.5
Cerebrospinal fluid glucose, mg/dL	26	85.0	56.0	-	130.0	19.4
Cerebrospinal fluid protein, mg/dL	26	89.5	44.0	-	214.0	35.3
Cerebrospinal fluid cells, cells/µL	26	1.0	1.0	-	11.5	2.1

	N	Yes	No
Clinical			
Gender, male	33	20	13
Diabetes, type 2	33	32	1
Insulin use	31	13	18
Retinopathy	17	4‡	13
Nephropathy	33	2	31
Cardiovascular disease	33	3	30

mo = month, N = number, NIS = Neuropathy Impairment Score, NS = not significant (p > 0.05), SD = standard deviation
‡ Nonproliferative retinopathy.

largely monophasic, the pain and weakness can persist for weeks, months, and even years. With time, the pain and weakness tend to improve without intervention, and, in a few cases, there may be complete resolution after months or years. However, some degree of residual pain or weakness usually persists. For example, at initial evaluation, more than 30/33 of our cohort of patients with DLRPN required an aid for walking and 50% of these patients still required it at follow-up. Patients do improve though and only three of the patients were still in wheelchairs at the time of their last evaluation. Proximal segment reinnervation and recovery tends to occur earlier and more completely (many patients are wheelchair dependent at evaluation but most do not remain so) in contrast to the distal segment for which longterm requirements for gait aids (ankle braces) are often needed.

PAINLESS DIABETIC MOTOR NEUROPATHY

Although pain usually is the most prominent early clinical feature, recently a smaller population of patients who have a similar anatomical distribution of involvement when compared to DLRPN but without prominent pain have been systematically identified and characterized. Indeed, in one early clinical description of DLRPN, Chokroverty and colleagues comment on some patients having a symmetrical, slowly progressive, and occasional painless process.[9] At that time, they (and others) suggested that the pathological basis of these cases was probably metabolic derangement.[9,10,40,43] Asbury further proposed that whereas the acute and asymmetrical cases were likely due to ischemic injury, the slower, more symmetrical cases might result from metabolic derangement.[3] Other authors have raised the question of whether chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is more common in diabetic patients than in the general population.[24,26,33,44] Amato and Barohn have noted that motor polyradiculoneuropathies without pain occur in DM[2] and questioned whether such cases are instances of CIDP occurring in diabetic patients. The reason why these patients might have CIDP is that they are motor predominant, present clinically as a polyradiculoneuropathy, and do not have pain—all features that are typical of "classical" CIDP.

To elicit the cause of this painless diabetic motor neuropathy, the author and colleagues identified and reviewed the clinical, electrophysiological, and pathological features a small cohort of 23 diabetic patients with a painless motor and lower-limb predominant polyneuropathy all who had undergone nerve biopsy. Evidence showed that the painless syndrome tends to begin insidiously (none had acute onset) and progresses at a slower pace. Compared to typical DLRPN, many more had bilateral onset with a more severe and widespread clinical course. There was more involvement of the upper limb segments and more severe involvement of the distal lower limb segments. However, these painless patients had problematic autonomic and sensory involvement of large and small fibers and frequently had substantial weight loss. Because CIDP patients suffer from a demyelinating neuropathy and autonomic fibers are mostly unmyelinated, CIDP patients should not develop much autonomic neuropathy.[20] Consequently, the large degree of autonomic involvement in these painless diabetic neuropathy patients would argue against their having CIDP. The NCS/needle EMG findings demonstrated axonal (as opposed to demyelinating) radiculoplexus neuropathies. Although this painless syndrome was mostly a generalized symmetrical proximal and distal process with a slow course (all typical of CIDP), the pattern of sensory involvement was panmodal (both large and small fiber), whereas CIDP is usually large fiber predominant.[12,25] In addition, the electrophysiology did not meet American Academy of Neurology CIDP electrophysiological criteria1 nor the author's institution's criteria for CIDP[34] in any cases.

Furthermore, the pathological specimens from this painless cohort had evidence of ischemic injury and microvasculitis. These findings were similar to those of DLRPN (see below) and different than the inflammatory demyelination typically seen in CIDP. As a result, this painless diabetic motor neuropathy is not correctly categorized clinically or physiologically as "diabetic CIDP," but it is more likely painless DLRPN and part of the clinical spectrum of DLRPN.[21]

DIABETIC CHRONIC INFLAMMATORYDEMYELINATING POLYRADICULONEUROPATHY

As noted earlier, some authors believe that the incidence and prevalence of CIDP is increased in diabetic patients. The question of whether the painless diabetic motor neuropathy patients really were diabetic CIDP was considered. It was concluded that they actually had painless DLRPN and not diabetic CIDP because their needle EMGs were axonal and not demyelinating, they had prominent autonomic involvement, and their pathology was that of ischemic injury and microvasculitis and not inflammatory demyelination.

To assess the association of DM and CIDP, the population of Olmsted County, Minnesota, (from 1982-2001) was reviewed and showed an incidence of CIDP of 1.6/100,000/year and a prevalence of 8.9/100,000 persons on January 1, 2000.34 Only one of 23 CIDP patients (4%) had DM, whereas 14 of 115 age- and gender-matched control patients (12%) had DM. Therefore, DM is unlikely to be a major risk covariate for CIDP, but a small effect cannot be excluded. Furthermore, the perceived association of DM with CIDP may be more likely due to misclassifications of other forms of diabetic neuropathy (such as DLRPN). A similar study of an Italian population also found no association between CIDP and DM.[8] Consequently, the data do not support a "diabetic CIDP."

DIABETIC THORACIC RADICULONEUROPATHY

Diabetic thoracic radiculoneuropathy usually begins with a band-like pain extending from the back or side of the body radiating anteriorly towards the chest or belly. The pain may be similar in character to that described in DLRPN (sharp-stabbing, burning, hurting, or allodynia). Patients also often describe a feeling of tightness and "asleep" or "prickling" numbness with associated allodynia localized to the abdominal or chest wall, making clothing uncomfortable. The thoracic symptoms may occur concurrently with DLRPN. Sometimes, the associated weakness can be recognized by a flaccid outpouching of the abdomen in the region of sensory disturbance.[6,37] Needle EMG may also reveal findings of denervation at the affected thoracic paraspinal levels.

Thermoregulatory sweat testing will often show a focal region of anhidrosis. This disorder shares many clinical features with herpes zoster radiculitis, except in herpes a vesicular eruption usually occurs. It is therefore important to closely examine the patient.

DIABETIC CERVICAL RADICULOPLEXUS NEUROPATHY

The syndrome of DCRPN is very similar to that of DLRPN except that the upper limbs and not the lower limbs are primarily involved. Diabetic cervical radiculoplexus neuropathy begins primarily with pain but evolves into a syndrome in which weakness is the main problem. Eighty-five DCRPN patients evaluated at the author's institution were recently retrospectively indentified.[36] They were middle to old age (median age 62 years) and the main presenting symptom was pain (53/85). At evaluation, weakness was the most common symptom (84/85) followed by pain (69/85) and numbness (56/85). Upper, middle, and lower plexus segments were involved equally (about half of cases) and panplexopathy was not unusual (25/85). This is in contrast to nondiabetic inflammatory brachial plexopathies in which the upper plexus is preferentially involved. Over half of patients (44/85) had at least one additional body region affected (30 contralateral cervical, 20 lumbosacral, and 16 thoracic) and so a widespread DRPN was present. This is also in contrast to nondiabetic inflammatory brachial plexus neuropathy in which involvement of other body regions is unusual. Recurrent disease occurred about 20% of the time (18/85). Electrophysiological studies showed an axonal neuropathy (80/80) with paraspinal denervation in one-third (21/65). Autonomic (23/24) and quantitative sensory (10/13) testing abnormalities were common. Magnetic resonance imaging showed abnormality of the brachial plexus in all cases (38/38) (often mild) usually with increased T_2 signal. At onset, DCRPN cases tended to be focal and unilateral but over time they often became more widespread and bilateral (like DLRPN). The association of DCRPN with DLRPN has also been noted by other authors.[15,27,38,42]

EPIDEMIOLOGY

There has not been a formal incidence study of DRPNs, but data from the Rochester Diabetic Neuropathy Study estimated a prevalence of 1% for DLRPN in patients with DM.[14] Epidemiological data regarding DTRN and DCRPN has not yet been published.

PATHOGENESIS OF DIABETIC RADICULOPLEXUS NEUROPATHIES

Over the years, it had been suggested that the pathophysiological basis of disease in diabetic patients who present with rapid evolving asymmetrical plexopathies is likely due to ischemic injury and most of the research in this area has centered on DLRPN.[3,15,28,29,35,39,40,42] In the author's prospective series of 33 patients with DLRPN, distal cutaneous nerve biopsies in affected patients showed characteristic findings of ischemia with multifocal fiber loss, perineurial degeneration or thickening, neovascularization and abortive regeneration of nerve fibers forming microfasciculi (injury neuroma) (Figure 1).[15] These findings were compared to nerves of patients with DPN, and those with DLRPN showed significantly more ischemic changes. Axonal enlargements were also noted on transverse nerve sections which were similar to enlargements described by others in experimental ischemia and were probably due to accumulated organelles.[16,31,32] Teased nerve fiber evaluation demonstrated increased rates of axonal degeneration and empty nerve strands when compared to normal control subjects as well as those with DPN.

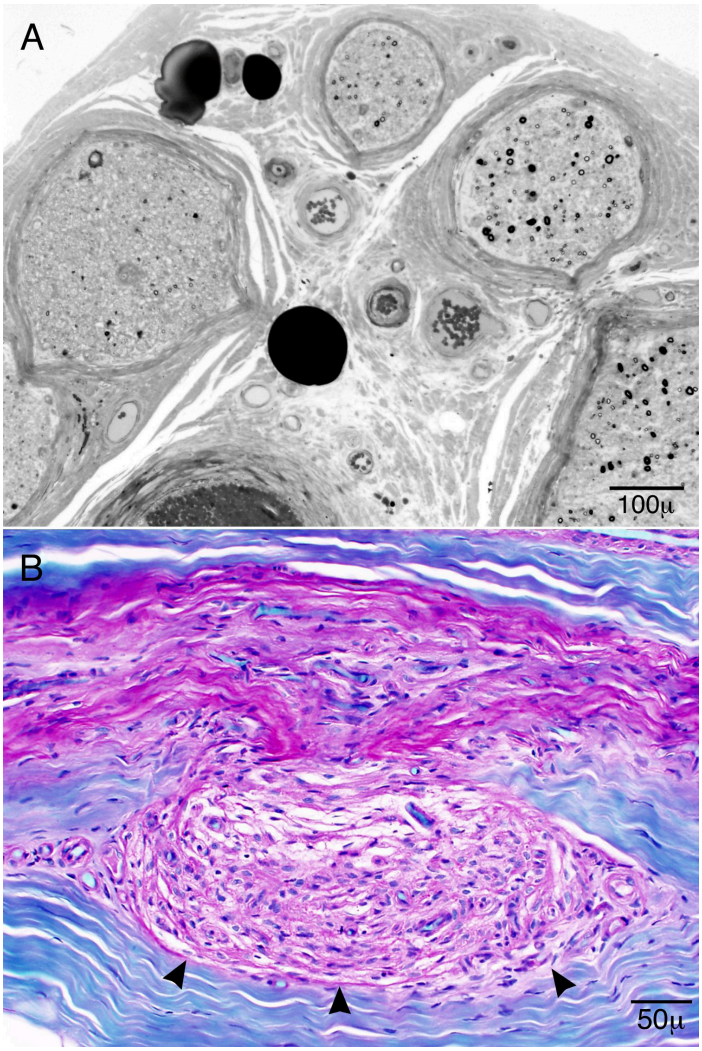

Figure 1. Transverse semithin epoxy section stained with methylene blue taken from patients with painless DLRPN. **(A)** The top panel shows multifocal fiber loss. The fascicle on the left and upper middle are devoid of fibers whereas as the two on the right still retain some myelinated fibers. **(B)** This is a longitudinal paraffin section stained with Luxol Fast Blue/Periodic Acid-Schiff showing damaged perineurium of the originating fascicle, resulting in leakage of endoneurial contents yielding an area of injury neuroma (within arrowheads). These findings are typical of ischemic injury due to microvasculitis as can be seen in both painless and painful DLRPN.
DLRPN = diabetic lumbosacral radiculoplexus neuropathy

Although segmental demyelination was observed on teased nerve fiber preparations, the rates were low and tended to be grouped demyelination along the length of single nerve fibers. These changes of grouped demyelination are typical findings of secondary segmental demyelination from axonal atrophy[11] as has been reported in DLRPN associated with ischemic injury[16]

and is not characteristic of inflammatory demyelination. In experimental models of ischemic injury, the nerve regions in which demyelination was found were at the margins of ischemia in regions where nerve fibers were damaged but survived. Nerve biopsies that show multifocal fiber loss contain the margins of ischemia (the transitional zone from axonal degeneration and reduced myelinated fiber density to regions of normal myelinated nerve fibers). In DLRPN, there was a significant association with multifocal fiber loss and increased rates of segmental demyelination. This association is evidence that the demyelination in DLRPN is likely secondary to ischemic injury.[18] The cause of the ischemic injury appears to be microvasculitis. In the author's prospective series there were inflammatory infiltrates in all nerve biopsies, hemosiderin-laden macrophages in most. Inflammation involving the vessel walls suggestive of microvasculitis was seen in half of the cases and in several biopsies diagnostic changes of microvasculitis were observed (Fig. 2).[16]

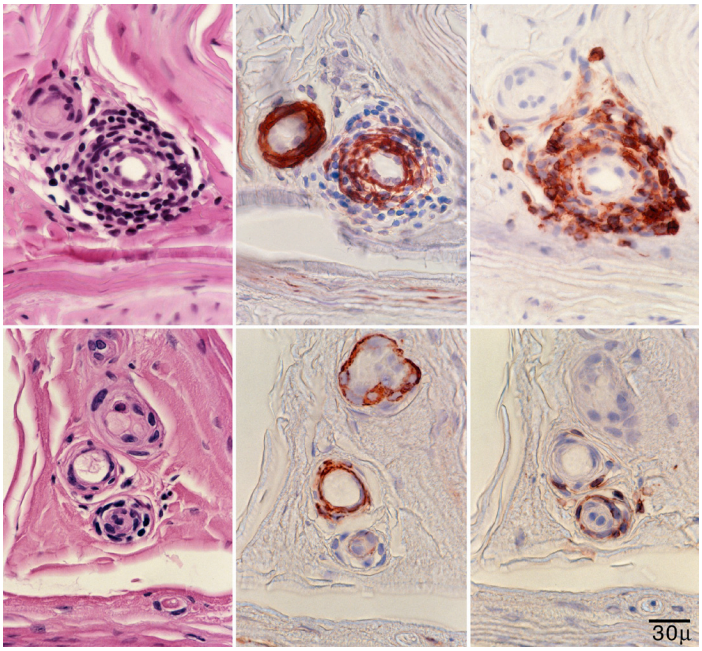

Figure 2. Serial skip paraffin sections from a patient with painful DLRPN. The left column sections are stained with hematoxylin and eosin, the middle column sections are stained with anti-smooth muscle actin, and the right columns sections have reacted with leukocyte common antigen (CD45). The upper row demonstrates fragmentation of the tunica media of the microvessel with mononuclear cells, demonstrative of focal microvasculitis seen in DLRPN. From Dyck.[47]
DLRPN = diabetic lumbosacral radiculoplexus neuropathy

Despite this understanding that typical painful DLRPN is due to altered immunity and microvasculitis, cases with slower, more symmetrical presentations were historically thought to be due to metabolic derangement as opposed to ischemia.[9] The hyperglycemic state is likely a risk factor for developing both or the symmetrical and asymmetrical forms of these neuropathies but is not the main mechanism. In the author's experience, DLRPN and related disorders appear to occur more frequently in those with mild type 2 DM as opposed to type 1 DM. When DLRPN patients were compared to a community cohort of diabetic patients, the DLRPN patients had fewer longterm complications of hyperglycemia (less retinopathy, nephropathy), better glucose control, and been diabetic for a shorter period of time.[18] Furthermore, these syndromes can occur in those without DM,[17] implying that prolonged hyperglycemia and metabolic abnormality is not a prerequisite for developing them.

Little is known about the pathological alterations in diabetic associated thoracic radiculoneuropathies. In the few cases studied by the author, the nerve has contained inflammatory cell infiltrates suggesting the possibility that this is also an immune disorder. There is a paucity of published literature on the pathology of DCRPN. A recently finished a study on DCRPN (Massie RM, Mauermann ML, Staff NP, Amrami KK, Mandrekar JN, Dyck PJ, Klein CJ, Dyck PJB. 2012; submitted for publication.) included nerve biopsies in some of these patients. The nerve biopsies (11 upper and 11 lower limbs) showed ischemic injury (axonal degeneration, multifocal fiber loss 15/22, focal perineurial thickening 16/22, and injury neuroma 5/22) and increased inflammation (epineurial perivascular inflammation 22/22, hemosiderin 6/22, vessel wall inflammation 14/22, and microvasculitis 5/22). From this it was concluded that DCRPN is due to ischemic injury usually from microvasculitis and that DCRPN shares many of the pathological features of DLRPN, providing evidence that they should be categorized together in the spectrum of DRPNs.

TREATMENT

There are no established evidence-based treatments or previously published therapeutic trials for any of the radiculoplexus neuropathies. Because of the pathological evidence that DLPRN, DTRN, and DCRPN probably are immune-mediated neuropathies caused by microvasculitis of the nerve, investigators have suspected that immunotherapy may be useful if employed early. The rationale behind the timing of this intervention is that the early acute-to-subacute phase of the illness is when the inflammatory phase is most likely to be active and, hopefully, before extensive and poorly reversible axonal degeneration has occurred. Some small treatment series in the literature seem to support this assertion. In one small case series of two patients presenting clinically with DLRPN and vasculitis observed on nerve biopsy, both reported improvement with oral prednisone.40 In a separate report, fifteen DLRPN patients were treated with various immunomodulatory treatments including intravenous immunoglobulin (IVIg) with prednisone, IVIg alone, prednisone with cyclophosphamide, and sole prednisone. All patients reported improvement although it was not distinguished if this improvement was clearly from the immune therapy or the expected spontaneous improvement of a monophasic condition.[33] Another group compared 12 patients with DLRPN who received some type of immune therapy (prednisone, IVIg, or plasma exchange) with 29 patients who did not. The authors found that most patients improved regardless of treatment but it appeared that the treated group improved to a greater extent and more rapidly.[38]

Unfortunately, these treatment results have not been universally consistent. Another group reported three patients whose disease progressed despite immune treatment.[46] They urged caution with using immunotherapy in these patients. Indeed, their concern has merit as giving glucocorticoids to diabetic patients may

be associated with a substantial deterioration in their glycemic control. In the author's cohort, patients with DLRPN usually have type 2 DM and their blood glucose is usually well controlled. Anecdotally, most of the author's patients to whom IV steroids have been administered have not had marked disruption in glycemic control after the infusions, and none to date have had a major complication related to steroids. As DTRNs and DCRPN are likely due to similar pathological mechanisms as DLRPN, the same treatment approaches can be considered, although even less data exists about the merit of such interventions in these patients. Controlled trials need to be conducted before widespread treatment with immune agents can be universally recommended. Despite the various reports of immune therapy, there has not been any standardization of corticosteroid dose employed in DRPNs. The range in dosing is quite high, with reports from 1000 mg IV methylprednisolone given weekly for at least 12 weeks[15] to oral prednisone given 50 mg daily, tapered over 3 weeks.[2]

To more firmly establish an approach to treatment in the DRPNs, a multicenter prospective treatment trial with IV methylprednisolone was conducted. In this study, two-thirds of DLRPN patients received 15 treatments of intravenous methylprednisolone beginning at 1 g three times the first week and then tapering to 250 mg every other week at the end and given over a 12-week period. Seventy-five patients were studied in four medical centers. All patients were examined and their neurological symptoms quantitated using the Neuropathy Impairment Score (NIS) (a global score of weakness, reflex, and sensory loss) on eight separate occasions (weeks 1, 6, 12, 24, 35, 52, and 104). The primary endpoint measured was improvement of the NIS[13] by four points. Secondary endpoints included quantitative sensory testing, quantitative autonomic testing, and electrophysiological testing.

There was no significant difference in the primary endpoint between the treatment and placebo groups. However, many of the secondary outcome measures, especially relating to pain and sensory symptoms were significantly improved in the treatment group. An important drawback in this study was late enrollment (up to 6 months) after patients had reached their disease nadir. This delay may have allowed irreparable axonal loss, supporting the need for an earlier treatment trial. However, the improvement in pain observed in this trial alone is justification for the use of IV methylprednisolone in this group.[19]

Aside from treating the underlying pathological mechanism with immune therapy, many patients require symptomatic treatment for ongoing pain. Often the initial symptoms of pain are so severe in these patients that the use of opioid medication is required. Neuropathic pain agents can also be helpful but usually are used in conjunction with opioids. It is very important to define clear limits of narcotic medications to avoid the development of addiction. Approaches to treat concurrent opioid-related constipation are also important. Patients need to be made aware that the goal of this type of therapy is to reduce pain to a tolerable level and ameliorate some degree of suffering, but that complete pain relief may be impossible. The patient should also be made aware, however, that the DRPN is a monophasic illness. Therefore, with time, they can expect their symptoms to improve, although they may not completely resolve. Physical and occupational therapy is a mainstay of therapy in this condition given the marked weakness often associated with all types of DRPN, and it should be instituted early. Many patients may have to modify their work environment during the course of the illness, but they should be encouraged to continue their daily activities to the best of their capacity. Depression is common in these patients due to new and often profound morbidity as well as pain and loss of an independent lifestyle. Again, reassurance that their symptoms will improve is key, but recognition and treatment of situational depression is also quite important.

CONCLUSION

Diabetic lumbosacral radiculoplexus neuropathy, DTRPN, and DCRPN are part of a broader category of DRPNs. All of these syndromes pathophysiologically are likely due to ischemic injury from altered immunity and microvasculitis. Immune therapy (especially IV methylprednisolone) may help treat these conditions in the early part of illness but is still under study. There is no evidence that CIDP is associated with DM. However, there is a painless motor predominant form of DLRPN that is still due to an inflammatory mechanism. Symptomatic treatment in the form of narcotics in combination with neuropathic agents for pain as well as physical therapy should be considered at recognition of the condition. Importantly, patients need to be reassured that these inflammatory DRPNs almost always are monophasic in nature, and though complete resolution usually will not occur, with time and maybe with immunotherapy, improvement can be expected.

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Diabetic Neuropathy CME Questions:

1. Which of the following are associated with treatment induced diabetic neuropathy:
   1. Painful small fiber neuropathy
   2. Autonomic neuropathy
   3. Early worsening retinopathy
   4. Worsening nephropathy

   A. Only 1 and 2 are correct
   B. 1, 2, and 3 are correct
   C. 1, 2 and 4 are correct
   D. All are correct

2. Treatment induced diabetic neuropathy:
   A. Is also referred to as 'insulin neuritis' because it only occurs with insulin use.
   B. Is associated with a gradual increase in neuropathic pain as glycosylated hemoglobin values decrease.
   C. Is associated with hyperlipidemia and hypertriglyceridemia.
   D. Is associated with neuropathic pain that lasts from 12-24 months.

3. Cardiovascular autonomic neuropathy in diabetes:
   A. Is seen in 50-75% of patients with longstanding diabetes.
   B. Can be associated with a resting tachycardia.
   C. Is diagnosed in the majority of patients using orthostatic blood pressure measurements.
   D. Results in a 5-fold increase in mortality.

4. Hypoglycemic unawareness is associated with all of the following except:
   A. An increase risk of future hypoglycemic episodes.
   B. Suppression of the catecholamine response to falling blood glucose.
   C. The intentional relaxing of glucose control to prevent recurrent hypoglycemia.
   D. Increased glucocorticoid release with falling blood glucose.

5. Diabetic autonomic neuropathy can manifest in the following ways:
   A. Impaired pupillary constriction.
   B. Gastroparesis.
   C. Resting tachycardia.
   D. Distal anhidrosis with proximal hyperhidrosis.

6. The larger improvements in neurologic function over 1 year of stable glucose control in patients with a history of treatment induced diabetic neuropathy who have type 1 diabetes (compared to those with type 2 diabetes) is likely related to all of the following reasons EXCEPT:
   A. Greater drop in glycosylated A1C value.
   B. Younger age.
   C. Fewer co-morbid medical problems such has hypertension and hyperlipidemia.
   D. Lower final glycosylated A1C value.

7. The USA FDA has approved which of these drugs for the prevention and treatment of diabetic sensorimotor polyneuropathy:
   A. Aldose reductase inhibitors.
   B. Myo-inositol supplementation.
   C. Antioxidants such as alpha-lipoic acid.
   D. None of the above.

8. Generalized diabetic polyneuropathy is classifiable into two types which are:
   A. Small fiber sensory and small fiber autonomic polyneuropathies.
   B. Diabetic polyneuropathy and diabetic sensorimotor polyneuropathy (DSPN).
   C. Typical (DSPN) and atypical (small fiber sensory and autonomic) diabetic polyneuropathy.
   D. Brun's Garland syndrome and lumbosacral radiculoplexus neuropathy.

9. Chronic hyperglycemia control has been shown to prevent diabetic sensorimotor polyneuropathy. This result was unequivocally demonstrated in:
   A. The Sydney Trial.
   B. The DCCT Trial.
   C. The SNORT Trial.
   D. The RDNS Trial.

10. In the recently published Olmsted County Impaired Glycemia (IG) Trial, IG (as represented by impaired glucose tolerance) was found to result in which of outcomes a – d? Provide the most correct answer.
    A. An unequivocal and large increase in prevalence of diabetic complications.
    B. A low increase of polyneuropathy but not of retinopathy or nephropathy.
    C. A low significant increase of retinopathy without an increase of polyneuropathy.
    D. No increase of any microvessel complication.

11. The characteristic alteration of endoneurial microvessels in diabetic polyneuropathy is:
    A. Thrombosis of microvessels.
    B. Platelet adhesion to endothelial cells.
    C. Thickened basement membranes.
    D. Pericyte degeneration and reduplication and displacement of pericyte basement membranes.

12. In diabetics with carpal tunnel syndrome which one of the following is correct?
    A. The risk increases with age and duration of diabetes.
    B. Sensory symptoms are few while the motor symptoms are prominent.
    C. Concomitant osteoarthritis of the wrist is always present and is a very important additional risk factor for CTS in these diabetics.
    D. The primary risk factor in these diabetics is obesity and not the diabetes per se.

13. The optimum treatment for a diabetic with very symptomatic CTS is:
    A. Long term use of a wrist splint.
    B. Corticosteroid injections into the carpal tunnel.
    C. Surgical decompression.
    D. None of the above because they are all ineffective in such a patient.

14. Regarding ulnar neuropathy at the elbow (UNE) in diabetics which one of the following is correct?
    A. There is a very clear increase in incidence of UNEs in diabetics.
    B. Such UNEs are often severe.
    C. Electrodiagnostic studies easily distinguish between a UNE and diabetic polyneuropathy in the hand.
    D. Surgical decompression is the treatment of choice.

15. Regarding common peroneal neuropathy (CPN) in diabetics which one of the following is correct?
    A. A clear risk factor is the increased body mass index frequently present in diabetics.
    B. A foot drop in a diabetic is so clearly the result of the diabetes and increased body mass index causing CPN that it is unnecessary to investigate the patient for other causes of foot drop.
    C. Surgical decompression of the CPN is the treatment of choice.
    D. An ankle-foot orthosis (foot drop splint) is an important aid to improved walking.

16. Regarding meralgia paresthetica (MP) in diabetics which one of the following is correct?
    A. In addition to the sensory symptoms, a frequent complaint is that of thigh muscle weakness.
    B. Diabetes mellitus has been shown to be such a significant risk factor that non-diabetics presenting with MP should be investigated for diabetes.
    C. Age and obesity are not risk factors.
    D. Most patients require surgical decompression in order to recover.

17. One of the main causes of the inflammatory neuropathies in diabetes mellitus is:
    A. Metabolic derangement causing reduplication of basement membrane of endoneurial microvessels
    B. Ischemic injury from microvasculitis
    C. Inflammatory demyelination causing a CIDP-like illness
    D. Large arteriole necrotizing vasculitis causing systemic disease

18. Diabetes mellitus is likely a risk factor for the development of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP):
    A. True
    B. False

19. Painless lower limb and motor predominant diabetic neuropathy is likely:
    A. Diabetic CIDP
    B. Due to lumbar spinal stenosis
    C. A form of a motor neuron disease that diabetic patients are at risk for developing
    D. A form of a diabetic radiculoplexus neuropathy

20. Diabetic Radiculoplexus Neuropathies:
    A. Involve roots, plexus and nerves in upper and lower limbs and the trunk to variable extents
    B. Exclusively involve the lumbosacral levels
    C. Exclusively involve the thoracic levels
    D. Exclusively involve the cervical levels